



## Complete Summary

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### **GUIDELINE TITLE**

Viral infections. In: Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children.

### **BIBLIOGRAPHIC SOURCE(S)**

Viral infections. In: Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), HIV Medicine Association of the Infectious Diseases Society of America, Pediatric Infectious Diseases Society, American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2008 Jun 20. p. 91-146.

### **GUIDELINE STATUS**

This is the current release of the guideline.

This guideline updates a previous version: Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 3;53(RR-14):1-92. [422 references]

### **\*\* REGULATORY ALERT \*\***

### **FDA WARNING/REGULATORY ALERT**

**Note from the National Guideline Clearinghouse (NGC):** This guideline references a drug(s) for which important revised regulatory and/or warning information has been released.

- [January 16, 2009 - Topical Anesthetics](#): The U.S. Food and Drug Administration (FDA) issued a public health advisory to remind patients, healthcare professionals, and caregivers about potentially serious hazards of using skin numbing products, also known as topical anesthetics, for relieving pain from mammography and other medical tests and conditions. FDA is concerned about the potential for these products to cause serious, life-threatening adverse effects, such as irregular heartbeat, seizures, breathing difficulties, coma and even death, when applied to a large area of skin or when the area of application is covered. See the Advisory for recommendations on safe use of these products.

## COMPLETE SUMMARY CONTENT

\*\* REGULATORY ALERT \*\*

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INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT

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## SCOPE

### DISEASE/CONDITION(S)

Viral infections associated with human immunodeficiency virus (HIV) exposure and infection, including:

- Cytomegalovirus infection
- Hepatitis B virus infection
- Hepatitis C virus infection
- Human herpesvirus-6 and-7 infection
- Human herpesvirus-8 infection
- Herpes simplex virus infection
- Human papillomavirus infection
- Progressive multifocal leukoencephalopathy
- Varicella-zoster virus infection

### GUIDELINE CATEGORY

Counseling  
Diagnosis  
Evaluation  
Management  
Prevention  
Risk Assessment  
Screening  
Treatment

### CLINICAL SPECIALTY

Family Practice  
Infectious Diseases  
Internal Medicine  
Obstetrics and Gynecology  
Pediatrics  
Preventive Medicine

## **INTENDED USERS**

Advanced Practice Nurses  
Allied Health Personnel  
Clinical Laboratory Personnel  
Health Care Providers  
Nurses  
Patients  
Pharmacists  
Physician Assistants  
Physicians  
Public Health Departments

## **GUIDELINE OBJECTIVE(S)**

- To provide evidence-based guidelines for treatment and prophylaxis of opportunistic infections among HIV-exposed and HIV-infected children
- To serve as a companion to the United States Public Health Service (USPHS)/Infectious Diseases Society of America (IDSA) *Guidelines for the Prevention of Opportunistic Infections Among HIV-Infected Adults*

## **TARGET POPULATION**

Human immunodeficiency virus (HIV)-exposed and HIV-infected infants, children, and adolescents living in the United States

## **INTERVENTIONS AND PRACTICES CONSIDERED**

### **Prevention/Screening/Counseling**

1. Preventing exposure, including counseling on avoidance of exposure and behavior modification
2. Screening for cytomegalovirus, hepatitis, and human papillomavirus
3. Preventing first episode of disease
  - Vaccination
  - Primary prophylaxis\*
  - Discontinuation of primary prophylaxis
4. Prevention of recurrence
  - Secondary prophylaxis\*
  - Discontinuation of secondary prophylaxis

### **Treatment/Management**

1. Antiviral therapy\*
2. Highly active antiretroviral therapy (HAART)
3. Monitoring and adverse events, including immune reconstitution inflammatory syndrome
4. Management of treatment failure

**\*Note:** Details of antiviral drug therapy and prophylaxis can be found in the "Major Recommendations" section of this summary and in Tables 1-6 of the original guideline document.

## MAJOR OUTCOMES CONSIDERED

- Incidence and prevalence of viral infections
- Incidence of viral coinfections
- Treatment response
- Adverse drug reactions
- Clinically relevant drug interactions
- Immune reconstitution inflammatory syndrome
- Mortality

## METHODOLOGY

### METHODS USED TO COLLECT/SELECT EVIDENCE

Searches of Electronic Databases

### DESCRIPTION OF METHODS USED TO COLLECT/SELECT THE EVIDENCE

Pediatric specialists with expertise in specific opportunistic infections were selected to review the literature since the last publication of the prevention and treatment guidelines.

### NUMBER OF SOURCE DOCUMENTS

Not stated

### METHODS USED TO ASSESS THE QUALITY AND STRENGTH OF THE EVIDENCE

Weighting According to a Rating Scheme (Scheme Given)

### RATING SCHEME FOR THE STRENGTH OF THE EVIDENCE

#### Quality of Evidence Supporting the Recommendations

**I:** Evidence from at least one randomized, controlled trial.

**II:** Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies, or dramatic results from uncontrolled experiments.

**III:** Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

### METHODS USED TO ANALYZE THE EVIDENCE

Systematic Review

### DESCRIPTION OF THE METHODS USED TO ANALYZE THE EVIDENCE

Not stated

## **METHODS USED TO FORMULATE THE RECOMMENDATIONS**

Expert Consensus

## **DESCRIPTION OF METHODS USED TO FORMULATE THE RECOMMENDATIONS**

The current document combines recommendations for prevention and treatment of opportunistic infections (OIs) in human immunodeficiency virus (HIV)-exposed and -infected children into one document; it accompanies a similar document on prevention and treatment of OIs among HIV-infected adults prepared by a separate group of adult HIV and infectious disease specialists. Both sets of guidelines were prepared by the Opportunistic Infections Working Group under the auspices of the Office of AIDS Research (OAR) of the national Institutes for Health. Pediatric specialists with expertise in specific OIs were selected to review the literature since the last publication of the prevention and treatment guidelines, conferred over a period of several months, and produced draft guidelines.

## **RATING SCHEME FOR THE STRENGTH OF THE RECOMMENDATIONS**

### **Rating Scheme for Prevention and Treatment Recommendations**

**A:** Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. **Should always be offered.**

**B:** Moderate evidence for efficacy - or strong evidence for efficacy but only limited clinical benefit - supports recommendation for use. **Should generally be offered.**

**C:** Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequence (e.g., drug toxicity, drug interactions) or cost of the treatment or under consideration. **Optional.**

**D:** Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should generally not be offered.**

**E:** Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. **Should never be offered.**

## **COST ANALYSIS**

A formal cost analysis was not performed and published cost analyses were not reviewed.

## **METHOD OF GUIDELINE VALIDATION**

Internal Peer Review

## DESCRIPTION OF METHOD OF GUIDELINE VALIDATION

Recommendations were reviewed and discussed by the Pediatric Opportunistic Infections (OI) Working Group at a meeting in Bethesda, Maryland, on June 25 – 26, 2007. The final document was prepared after this meeting, reflecting the discussion and further revisions at that meeting.

## RECOMMENDATIONS

### MAJOR RECOMMENDATIONS

The quality of evidence supporting the recommendations (I-III) and the rating scheme for the recommendations (A-E) are defined at the end of the "Major Recommendations" field.

Refer to the original guideline document for information on epidemiology, clinical manifestations, and diagnosis of viral infections in human immunodeficiency virus (HIV)-exposed and HIV-infected children.

#### **Viral Infections: Cytomegalovirus**

##### **Prevention Recommendations**

###### *Preventing Exposure*

HIV-exposed infants and HIV-infected children, adolescents, and adults who are seronegative for cytomegalovirus (CMV) and require blood transfusion should be administered only CMV antibody-negative or leukocyte-reduced cellular blood products in nonemergency situations **(BIII)**.

Beginning at 1 year of age, CMV antibody testing on an annual basis is recommended for CMV-seronegative HIV-infected infants and children who are severely immunosuppressed (e.g., CD4 count  $<100$  cells/mm<sup>3</sup> or CD4 percentage  $<10\%$ ) **(BII)**. Annual testing will allow identification of children who have acquired CMV infection and might benefit from screening for retinitis.

HIV-infected adults and adolescents who are child care providers or parents of children in child care facilities should be informed that they are at increased risk for acquiring CMV infection **(BI)**. Risk for acquiring CMV infection can be diminished by optimal hygienic practices (e.g., hand-washing) **(AII)**.

###### *Preventing First Episode of Disease*

The primary method for preventing severe CMV disease is recognition of the early manifestations of the disease and prevention of the development of severe immunosuppression by treating with highly active antiretroviral therapy (HAART). HIV-infected children aged  $<5$  years who are CMV infected and severely immunosuppressed (e.g., CD4 count  $<50$  cells/mm<sup>3</sup> or CD4 percentage  $<5\%$ ) should have a dilated retinal examination performed by an ophthalmologist every 6 months **(AIII)**. Older children should be counseled to be aware of "floaters" in

the eye and visual changes, similar to the recommendation for adults **(BIII)**. In the HAART era, CMV end-organ disease has diminished to such an extent that primary prophylaxis with antiviral agents in HIV/CMV-coinfected people is generally not recommended **(CIII)**. CMV end-organ disease is best prevented by using antiretroviral therapy to maintain CD4 count  $>100$  cells/mm<sup>3</sup>. If this is not possible, prophylaxis with valganciclovir can be considered for HIV-infected adolescents who are CMV seropositive, have a CD4 count of  $<50$  cells/mm<sup>3</sup>, and are large enough to receive adult doses of valganciclovir **(CI)**.

#### *Discontinuing Primary Prophylaxis*

Since primary prophylaxis with antiviral agents in HIV/CMV-coinfected people is not recommended (as discussed above) no consideration of discontinuing primary prophylaxis is necessary.

### **Treatment Recommendations**

#### *Treatment of Disease*

Treatment of newborns with symptomatic congenital CMV disease involving the central nervous system (CNS) with intravenous ganciclovir for 6 weeks has been evaluated in a series of clinical trials conducted by the National Institute of Allergy and Infectious Diseases (NIAID) Collaborative Antiviral Study Group (CASG); all babies in these studies were HIV uninfected. Babies receiving therapy cleared their urine of CMV by culture by the end of the 6-week treatment period, although all experienced a rebound in their viruria following antiviral discontinuation. In a phase III, randomized, controlled trial, babies receiving intravenous ganciclovir for 6 weeks were less likely to have hearing deterioration over the first 2 years of life compared with babies receiving no antiviral therapy. Treated babies also had more rapid resolution of liver enzyme abnormalities and a greater degree of growth during the course of therapy. They also experienced fewer neurodevelopmental delays at 1 year of life compared with nontreated subjects. However, approximately two-thirds of the infants developed substantial neutropenia during therapy. In patients developing neutropenia, 48% required dose modification but most were able to complete the 6 weeks of therapy. Based upon these results, intravenous ganciclovir therapy (6 mg/kg/dose administered every 12 hours) for 6 weeks should be offered to HIV-exposed or HIV-infected babies with symptomatic congenital CMV disease involving the CNS **(BI)**. If during the 6 weeks of therapy a baby is confirmed to be HIV infected, some experts then would recommend a longer duration of treatment ( $>6$  weeks) **(BIII)**.

Management of CMV retinitis should be done in concert with an experienced ophthalmologist. Intravenous ganciclovir, oral valganciclovir, intravenous foscarnet, intravenous cidofovir, and the ganciclovir intraocular implant coupled with valganciclovir are all effective treatments for CMV retinitis in HIV-infected adults **(AI)**. For HIV-infected children the drug of choice for initial treatment for CMV retinitis as well as other end-organ disseminated CMV disease (e.g., colitis, esophagitis, and central nervous system [CNS] disease) is intravenous ganciclovir **(AI)**. Oral valganciclovir, a prodrug of ganciclovir, is one of the first-line treatments for HIV-infected adults with CMV retinitis **(AI)**. The drug is well absorbed from the gastrointestinal (GI) tract and rapidly metabolized to

ganciclovir in the intestine and liver. However, data on appropriate dosage of this drug for children are limited. Additionally, a valganciclovir liquid formulation is not commercially available. While extemporaneously compounded valganciclovir "recipes" are available, the pharmacokinetics, bioavailability, safety, and shelf-life of such formulations are unknown and they should not be used in pediatric patients. Thus, oral valganciclovir is an option primarily for older children who are large enough to receive the adult dose and tablet formulation of valganciclovir **(CIII)**.

An alternative drug to treat CMV disease or for use in ganciclovir-resistant CMV infections in HIV-infected children is foscarnet **(AI)**. Foscarnet employed as suppressive therapy has been associated with increased length of survival relative to ganciclovir in HIV-infected adult patients. Doses should be modified among patients with renal insufficiency.

Combination therapy with ganciclovir and foscarnet delays progression of retinitis in certain patients failing monotherapy and can be used as initial therapy among children with sight-threatening disease **(BIII)**. Combination therapy also has been used for adult patients with retinitis that has relapsed on single-agent therapy. Combination therapy with intravenous ganciclovir and foscarnet may also be considered in initial therapy of CMV CNS disease **(BII)**. However, combination therapy is associated with substantial rates of adverse effects.

Before the availability of valganciclovir, oral ganciclovir in combination with an intraocular ganciclovir implant had been used for maintenance treatment of CMV retinitis in adults. Given the lack of commercial availability of oral ganciclovir, its use in children can no longer even be considered.

In adults, the combination of oral valganciclovir with a ganciclovir sustained release intraocular implant, replaced every 6 to 9 months, was superior to daily intravenous ganciclovir in preventing relapse of retinitis and is preferred by some adult HIV specialists for patients with CMV lesions adjacent to the optic nerve or fovea **(AI)**. This regimen can be considered for treatment and chronic suppression of CMV retinitis in older children who are large enough to receive the adult dose and tablet formulation of valganciclovir.

Cidofovir is effective in treating CMV retinitis among adult patients who are intolerant of other therapies. However, cidofovir has not been studied in pediatric patients with CMV disease **(CIII)**.

Intravitreal injections of ganciclovir, foscarnet, or cidofovir have been used for control of retinitis but require biweekly intraocular injections. Data are limited in children, and biweekly injection is impractical for use in most children **(DIII)**. Implantation of an intravitreal ganciclovir medication release device in the posterior chamber of the eye also has been used in HIV-infected adults and adolescents. In HIV-infected adults with CMV retinitis, ganciclovir intraocular implant plus oral valganciclovir is superior to once-daily intravenous ganciclovir for preventing relapse of CMV retinitis. Intraocular implant plus intravenous ganciclovir or oral valganciclovir may be the preferred initial treatment for patients with immediate sight-threatening infections (e.g., adjacent to the optic nerve or fovea). Small peripheral lesions may be treated with systemic therapy without local treatment **(BII)**. Intraocular implants should not be used in children

<3 years of age because of the small size of the eyes in young children **(EIII)**. Intraocular cidofovir is not recommended in children because of lack of data and the risk of hypotonia observed in adults.

For CMV neurological disease, initiating therapy promptly is critical for an optimal clinical response. However, concentrations of ganciclovir in the CNS range from 24%–70% of those in the plasma, with brain concentrations of approximately 38% of plasma levels; hence combination treatment with ganciclovir and foscarnet might be preferred as initial therapy to stabilize disease and maximize response **(BII)**. However, this approach is associated with substantial rates of adverse effects, and optimal treatment for neurologic disease in children receiving optimized HAART is unknown.

#### *Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome*

Management of CMV retinitis should be done in concert with an experienced ophthalmologist. Recommendations for HIV-infected adults include indirect ophthalmoscopy through a dilated pupil performed at the time of diagnosis of CMV retinitis, after completion of induction therapy, 1 month after the initiation of therapy, and monthly thereafter while the patient is on anti-CMV treatment; recommendations should be similar for HIV-infected children with CMV retinitis **(AIII)**. Monthly fundus photographs, using a standardized photographic technique that documents the appearance of the retina, provide the optimum method for following patients and detecting early relapse **(AIII)**. For patients who have experienced immune recovery, the frequency of ophthalmologic follow-up can be decreased to every 3 months. However, because relapse of the retinitis occurs among patients with immune recovery, regular ophthalmologic follow-up still is needed.

The major side effects of ganciclovir and valganciclovir are myelosuppression (i.e., anemia, neutropenia, and thrombocytopenia) and renal toxicity. Dose reduction or interruption due to hematologic toxicity may be necessary in up to 40% of patients receiving intravenous ganciclovir; granulocyte colony-stimulating factor can be used to ameliorate marrow suppression. The main toxicities of foscarnet are decreased renal function and metabolic derangements. Renal toxicity and foscarnet binding to divalent metal ions such as calcium lead to metabolic abnormalities in approximately one-third of patients, and serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures, cardiac dysrhythmias, abnormal liver transaminases, and CNS symptoms can occur. Metabolic disturbances can be minimized if foscarnet is administered by slow infusion, with rates not exceeding 1 mg/kg/minute. Concomitant use of other nephrotoxic drugs increases the likelihood of renal dysfunction associated with foscarnet therapy. For patients receiving ganciclovir or foscarnet, monitoring of complete blood counts and serum electrolytes and renal function should be performed twice weekly during induction therapy and once weekly thereafter **(AIII)**.

The major side effect of cidofovir is potentially irreversible nephrotoxicity; the drug produces proximal tubular dysfunction including Fanconi syndrome and acute renal failure. When present, renal toxicity manifests as proteinuria and glycosuria. To minimize nephrotoxicity, probenecid should be administered before each

infusion, and intravenous hydration with normal saline should be administered before and after each cidofovir infusion. For patients receiving intravenous cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected. Other reported adverse events include anterior uveitis and ocular hypotony; serial ophthalmologic monitoring for anterior segment inflammation and intraocular pressure is needed while receiving the drug systemically. Cidofovir should not be administered concomitantly with other nephrotoxic agents. Cidofovir therapy must be discontinued if serum creatinine increases  $\geq 0.5$  mg/dL above baseline.

Immune recovery uveitis is an immunologic reaction to CMV associated with inflammation in the anterior chamber and/or the vitreous in the setting of immune recovery after initiation of effective HAART. Ocular complications of uveitis include macular edema and development of epiretinal membranes that can cause loss of vision. Immune recovery uveitis may respond to periocular corticosteroids or a short course of systemic steroids. Oral valganciclovir was beneficial in one small uncontrolled study.

### *Management of Treatment Failure*

Resistant strains of CMV should be suspected when progressive disease and continued recovery of virus occur despite ganciclovir therapy. Foscarnet is the drug of choice when ganciclovir resistance is suspected **(AI)**.

In patients with CMV retinitis, while drug resistance occurs among patients receiving long-term therapy, early relapse may be due to the limited intraocular penetration of systemically administered drugs; in HIV-infected adults, the placement of a ganciclovir implant in a patient who has relapsed while receiving systemic treatment is recommended because it achieves greater drug levels in the eye and often will control the retinitis for 6 to 8 months until the implant requires replacement **(BIII)**. Due to the size requirements of the implants, this option would be limited to older children with CMV retinitis. Many experts would initially treat early first relapse of retinitis with reinduction with the same drug followed by reinstitution of maintenance therapy **(AII)**. However, if drug resistance is suspected or if side effects or toxicities interfere with optimal courses of the initial agent, change to an alternative drug is reasonable **(AIII)**. Combination ganciclovir and foscarnet can be considered but is accompanied by greater toxicity **(BI)**.

### **Prevention of Recurrence**

CMV disease is not cured with courses of available antiviral agents (e.g., ganciclovir, foscarnet, or cidofovir). After induction therapy, the standard recommendation has been to provide secondary prophylaxis (chronic maintenance therapy) for the remainder of the person's life **(AI)**. Regimens that can be considered for chronic suppression in adults and adolescents include intravenous ganciclovir, oral valganciclovir, intravenous foscarnet, combined intravenous ganciclovir and foscarnet, parenteral cidofovir, and (for retinitis only) ganciclovir administration via intraocular implant **(AI)**. Because of more limited data on drug pharmacokinetics and dosing in children, intravenous ganciclovir or foscarnet are the preferred secondary prophylaxis regimens for children; oral valganciclovir can

be considered for older children able to receive adult dosing. Repetitive intravitreal injections of ganciclovir, foscarnet, and cidofovir have been reported to be effective for secondary prophylaxis of CMV retinitis, although intraocular therapy alone does not provide protection to the contralateral eye or to other organ systems and therefore typically is combined with systemic treatment. Additionally, frequent intravitreal injections are impractical for use in most children **(DIII)**.

The choice of a chronic maintenance regimen for patients treated for CMV disease should be made in consultation with a specialist. Chronic maintenance therapy is not routinely recommended for gastrointestinal (GI) disease but should be considered if relapses occur **(BII)**. A role for maintenance therapy for CMV pneumonitis has not been established **(CIII)**. For patients with retinitis, decisions should be made in consultation with an ophthalmologist and should take into consideration the anatomic location of the retinal lesion, vision in the contralateral eye, and the immunologic and virologic status of the patient **(BIII)**. Intraocular implants should not be used in children <3 years of age because of the small size of the eyes in young children **(EIII)**.

#### *Discontinuing Secondary Prophylaxis*

Multiple case series have reported that maintenance therapy can be discontinued safely among adult and adolescent patients with CMV retinitis whose CD4 counts have indicated a sustained increase in response to HAART. These patients have remained disease free for >30 to 95 weeks, whereas during the pre-HAART era, retinitis typically reactivated in <6 to 8 weeks after stopping CMV therapy. Plasma HIV RNA levels were variable among these patients, supporting the hypothesis that CD4 count is the primary determinant of immune recovery to CMV. CMV retinitis can occur in HAART-treated adults with high CD4 counts, however, suggesting that CMV-specific cellular immunity may be important in controlling CMV in immune-reconstituted HIV-infected adults. In HIV-infected adults with CMV retinitis, discontinuing secondary prophylaxis is considered for patients with a sustained increase in CD4 count to >100 cells/mm<sup>3</sup> in response to treatment.

The safety of discontinuing secondary prophylaxis following immune reconstitution with HAART in HIV-infected children has not been as well studied. Low or undetectable HIV replication in children is the strongest correlate with CMV immune reconstitution, being associated with a higher frequency of CMV-specific CD4 cells. Early institution of HAART may assist in controlling CMV infection through maintenance of normal CD4 count and cytotoxic T-lymphocyte responses in HIV-infected children. In deciding whether to discontinue secondary prophylaxis, one also must consider the significant toxicities that can be associated with currently available antiviral drugs active against CMV, including those seen in *in vitro* and animal models.

Recognizing the limitations of the pediatric data but drawing upon the growing experience in adult patients, discontinuing prophylaxis may be considered for pediatric patients aged 1 to 6 years who are receiving HAART therapy and have a sustained (e.g., >6 months) increase in CD4 count to >500 cells/mm<sup>3</sup> or CD4 percentage to >15%, and for children aged >6 years, an increase in CD4 count to >100 cells/mm<sup>3</sup> or CD4 percentage to >15%, as for adults **(CII)**. Such decisions should be made in close consultation with an ophthalmologist and should take into

account such factors as magnitude and duration of CD4 cell increase, anatomic location of the retinal lesion, vision in the contralateral eye, and the feasibility of regular ophthalmologic monitoring **(CIII)**.

All patients who have had anti-CMV maintenance therapy discontinued should continue to undergo regular ophthalmologic monitoring at least 3 to 6 month intervals for early detection of CMV relapse, as well as for immune reconstitution uveitis **(AII)**. CMV viral load or other markers of CMV infection (e.g., antigenemia or viral deoxyribonucleic acid [DNA] tests) are not well standardized; their role in predicting relapse remains to be defined and they are not recommended for routine monitoring **(DIII)**.

#### *Re-Initiating Secondary Prophylaxis*

Relapse of CMV retinitis occurs among adult patients whose anti-CMV maintenance therapies have been discontinued and whose CD4 counts have decreased to  $<50$  cells/mm<sup>3</sup>; reinstitution of secondary prophylaxis is recommended for HIV-infected adults when CD4 count falls to  $<100$  cells/mm<sup>3</sup>. For HIV-infected children in whom secondary prophylaxis has been discontinued due to immune reconstitution, secondary prophylaxis should be reinstituted in children aged 1 to 6 years when the CD4 count has decreased to  $<500$  cells/mm<sup>3</sup> or CD4 percentage to  $<15\%$ , and for children aged  $>6$  years when CD4 count decreases to  $<100$  cells/mm<sup>3</sup> or CD4 percentage to  $<15\%$  **(BIII)**.

### **Viral Infections: Hepatitis B Virus (HBV)**

#### **Prevention Recommendations**

##### *Prevention of Exposure*

All pregnant women, including HIV-infected women, should be tested for hepatitis B surface antigen (HBsAg) during an early prenatal visit in each pregnancy **(AI)**. Testing should be repeated in late pregnancy for HBsAg-negative women at high risk for HBV infection (e.g., injection drug users, those with intercurrent sexually transmitted infections, and those with multiple sexual partners). Pregnancy is not a contraindication to hepatitis B vaccination for women who have not been previously vaccinated; current hepatitis B vaccines contain noninfectious HBsAg and should cause no risk to the fetus.

##### *Preventing First Episode of Disease*

All infants born to HBV-infected women, including HIV-coinfected women, should receive hepatitis B vaccine and hepatitis B immune globulin (HBIG) within 12 hours of birth, a second dose of hepatitis B vaccine at age 1 to 2 months, and a third dose at age 6 months **(AI)** (Figures 1 and 2 in the original guideline document). For preterm infants weighing  $<2,000$  g, the initial vaccine dose (birth dose) should not be counted as part of the vaccine series because of the potentially reduced immunogenicity of hepatitis B vaccine in these infants; three additional doses of vaccine (for a total of four doses) should be administered beginning when the infant reaches age 1 month. A three-dose hepatitis B vaccine regimen is 95% effective in preventing HBV infection in HBV-exposed infants.

Post-vaccination testing for hepatitis B surface antibody (anti-HBs) and HBsAg should be performed at age 9 to 18 months among infants born to HBsAg-positive women. The level of anti-HBs that is considered to be protective is >10 mIU/mL. Infants who are HBsAg negative and have anti-HBs levels <10 mIU/mL should be revaccinated with a second three-dose series of hepatitis B vaccine and retested 1 to 2 months after the final dose of vaccine.

The three-dose series of hepatitis B vaccine is also recommended for all children and adolescents aged <19 years who were not previously vaccinated, including HIV-infected children. However, diminished antibody responses to hepatitis B vaccination may be seen in HIV-infected children, especially in older children or those with CD4 counts <200 cells/mm<sup>3</sup>. For this reason, HIV-infected infants, children, and adolescents should be tested for anti-HBs 1 to 2 months after completing the vaccination series, and if anti-HBs levels are <10 mIU/mL, revaccinated with a second three-dose series of hepatitis B vaccine. Modified hepatitis B vaccine dosing regimens, including a doubling of the standard antigen dose, might increase response rates. However, although a current randomized trial is evaluating the use of various hepatitis B vaccine preparations and doses in HIV-infected youth, no data are available at this time.

The need for booster doses of hepatitis B vaccine in HIV-infected persons has not been determined. Annual anti-HBs testing and booster doses when the anti-HBs levels decline to <10 mIU/mL should be considered in persons with ongoing risk of hepatitis B exposure.

All children, including HIV-infected children and those with HBV coinfection, should receive hepatitis A vaccination at age 1 year (i.e., 12 to 23 months), with the two doses in the series administered ≥6 months apart. Children who are not vaccinated by age 2 years can be vaccinated at subsequent visits (Figures 1 and 2 in the original guideline document).

HBV-infected children should be advised not to share toothbrushes or other personal care articles that might be contaminated with blood. Although efficiency of sexual transmission of HBV is relatively low, safe-sex practices should be encouraged for all HIV-infected adolescents and young adults; barrier precautions (e.g., latex condoms) are recommended to reduce the risk for exposure to sexually transmitted pathogens including HBV.

## **Treatment Recommendations**

### *Treatment of Disease*

#### General Issues

Individualization of therapy is essential for any HBV-infected child and should be based upon the child's age, age at acquisition of infection, HBV DNA levels, and serum transaminase levels. Antiviral therapy regimens for chronic hepatitis B are currently approved only for children >2 years of age with compensated liver disease.

Children infected with HBV who are not receiving anti-HBV therapy should be closely monitored with determination of serum aminotransferase levels every 6 months. If persistent elevation of serum transaminase levels is seen (more than 2-fold the upper limit of normal for  $\geq 6$  months), hepatitis B early antigen (HBeAg), antibodies to HBeAg (anti-HBe), and HBV DNA levels should be obtained. Monitoring of serum transaminases and HBV DNA levels over time is important before the initiation of antiviral therapy to identify patients who may be in the process of spontaneous HBeAg seroconversion who would not require treatment. Liver biopsy is not required prior to treatment but may be helpful in determining the severity of hepatic inflammation and fibrosis and to exclude other causes of liver disease.

There are no clear-cut recommendations for the treatment of chronic childhood HBV infection. HBV-infected children often have milder disease than adults and may show spontaneous HBeAg seroconversion. There are few large randomized controlled trials of antiviral therapies for chronic hepatitis B infection in childhood. Moreover, the long-term safety of many of the agents used in the treatment of chronic hepatitis B infection in adults is not known in children. However, a 2004 consensus meeting of pediatric liver experts recommended that antiviral treatment be considered in children with chronic HBV infection who have necroinflammatory liver disease for  $>6$  months duration.

Indications for treatment of chronic HBV infection in HIV-coinfected children are the same as in HBV-infected children without HIV infection and include (1) evidence of ongoing HBV viral replication, as indicated by the presence of detectable serum HBV DNA, with or without HBeAg positivity, for  $>6$  months; and (2) persistent elevation of serum transaminase levels (at least twice the upper limit of normal for  $>6$  months); or (3) evidence of chronic hepatitis on liver biopsy **(BII)**. Children without necroinflammatory liver disease usually do not warrant antiviral therapy **(DIII)**. Treatment is not currently recommended for children with immunotolerant chronic HBV infection (i.e., normal serum transaminase levels despite detectable HBV DNA) **(DIII)**. The goals of treatment in children with chronic hepatitis B infection are identical to those in adults and include suppression of HBV replication, normalization of serum transaminase levels, acceleration of HBeAg seroconversion, preservation of liver architecture, and prevention of long-term sequelae such as cirrhosis and hepatocellular carcinoma (HCC).

At the present time, the optimal agent and duration of therapy of childhood hepatitis B infection remain unclear. Treatment of chronic hepatitis B infection is evolving; consultation with providers with expertise in treating chronic hepatitis B infection in children is recommended.

#### Treatment of Chronic Hepatitis B Infection in Adults and Adolescents

To date, six medications have been approved for treatment of chronic hepatitis B infection in adults. These include interferons (both standard and pegylated), nucleoside analogues such as lamivudine, telbivudine, entecavir, and the nucleotide analogue adefovir. U.S. Food and Drug Administration (FDA)-approved HIV antiretroviral medications, such as tenofovir and emtricitabine, also have significant activity against HBV, although they are not approved for this indication. Preferred initial therapies for adults with chronic hepatitis B without HIV infection

include pegylated interferon-alfa, entecavir, or adefovir monotherapy. In adults with chronic hepatitis B infection with or without HIV infection, treatment for hepatitis B is considered in HBeAg-positive individuals with HBV DNA  $\geq 20,000$  IU/mL ( $>10^5$  copies/mL), HBeAg-negative persons with HBV DNA  $\geq 2,000$  IU/mL ( $>10^4$  copies/mL), patients with persistent serum transaminase elevation, or patients undergoing liver biopsy with evidence of cirrhosis or fibrosis.

Treatment options for HBV in the setting of HIV infection must take into account the goals of therapy and the impact treatment may have on both HIV and HBV replication. In coinfecting patients who require treatment for chronic hepatitis B, HIV, or both infections, many experts would initiate a fully suppressive regimen for treatment of HIV infection that includes a dual nucleoside analogue backbone with drugs that have dual activity against both HIV and HBV plus a third agent with activity against HIV; this approach may reduce the risk of IRIS, particularly in patients with advanced immune deficiency. Tenofovir plus lamivudine or emtricitabine would be the first-choice option for the nucleoside backbone; the combination of tenofovir with lamivudine was demonstrated to be more effective in suppressing HBV than either drug alone and prevents development of lamivudine resistance. In the instances where HIV treatment is not an option but treatment of hepatitis B infection is needed, pegylated interferon-alfa may be used alone as it does not lead to the development of drug-resistant HIV or HBV mutants. The use of tenofovir, lamivudine, or emtricitabine without a fully suppressive HAART regimen should be avoided because of the rapid development of drug-resistant HIV mutations.

#### Treatment of Chronic Hepatitis B Infection in Children without HIV Infection

Only two drugs (monotherapy with interferon-alfa [standard] or lamivudine) are currently FDA approved for treatment of chronic hepatitis B in children **(AI)**. Pediatric trials of these agents are limited but show that although these medications are well tolerated by children, response rates are low and HBV infection is not fully eradicated by treatment. In HIV-uninfected children, HBeAg seroconversion rates after 1 year of treatment are similar. Interferon-alfa treatment is given for only 6 months, but requires subcutaneous administration and has more frequent side effects including growth impairment. Although lamivudine is administered orally and has a lower rate of side effects, it requires a longer duration of therapy and has a high rate of resistance if taken for an extended period of time.

Although various combination regimens involving sequential or concurrent lamivudine and standard or pegylated interferon-alfa have been studied in children or adults with chronic hepatitis B, the superiority of combination therapy over monotherapy with standard or pegylated interferon-alfa or lamivudine has not been demonstrated, although lamivudine resistance rates may be lower. A recent study of children with immunotolerant HBV infection suggested possible benefit from sequential lamivudine and interferon-alfa therapy, with 78% of patients clearing HBV DNA by the end of treatment. However, at this time, combination therapy cannot be recommended for pediatric HBV infection until more data are available **(DII)**.

#### Treatment of HIV/HBV-Coinfected Children

None of the clinical studies of treatment of chronic hepatitis B infection have specifically studied children with HIV/HBV coinfection. As in coinfecting adults, choice of antiviral therapy for the HIV/HBV-coinfecting child involves consideration of whether concurrent HIV treatment is warranted.

- If treatment of chronic hepatitis B but not HIV infection is indicated, standard interferon-alfa would be the preferred agent **(BIII)**. Adefovir could also be considered in older children able to receive adult dosing **(BIII)**. Antiviral drugs with activity against HIV (e.g., lamivudine, emtricitabine, tenofovir, and possibly entecavir) should be avoided to prevent the future development of drug-resistant HIV mutations.
- If treatment of HIV infection but not chronic hepatitis B is indicated, use of a HAART regimen that avoids the use of drugs with activity against HBV (e.g., lamivudine, emtricitabine, or tenofovir) is recommended to prevent the future development of HBV drug resistance **(BIII)**. Alternatively, in older coinfecting children who can receive tenofovir, use of a HAART regimen with a nucleoside analogue backbone that contains two drugs effective against HBV (tenofovir plus lamivudine or emtricitabine) can be considered **(BIII)**.
- If treatment of both HIV and chronic hepatitis B is indicated and the child is naïve to lamivudine, an antiretroviral regimen that includes lamivudine (or emtricitabine) is recommended **(BIII)**. A regimen containing tenofovir and a nucleoside analogue (either lamivudine or emtricitabine) is preferred for HIV/HBV-coinfecting adults and should be considered for use in older HIV-infected children or adolescents who can receive adult dosage. However, tenofovir is not approved for use in HIV-infected children <18 years and there is no pediatric formulation currently available. While pediatric studies with an investigational pediatric formulation of tenofovir are under way, data are not yet available.
- If treatment for HIV and chronic hepatitis B is indicated and the child is receiving antiretroviral therapy including lamivudine or emtricitabine with HIV suppression but detectable plasma HBV DNA, HBV lamivudine resistance can be assumed. However, HBV drug-resistant isolates may have lower replicative capacity and although controversial, some experts recommend continued use of lamivudine or emtricitabine **(CIII)**. Treatment options for such children who require HBV therapy include the addition of interferon therapy to the antiretroviral regimen **(BIII)**, or tenofovir **(BIII)**, or adefovir if the child can receive adult dosing **(BIII)**. There are insufficient data on other anti-HBV drugs in children to make recommendations.

### Interferons

Standard interferon-alfa-2a or -2b is the therapy that has received the most study in children with chronic hepatitis B (without HIV infection) and is recommended for the treatment of chronic hepatitis B infection with compensated liver disease in children without HIV infection aged ≥2 years who warrant treatment **(BII)**. In a review of 6 randomized clinical trials in 240 HBV-infected children aged >1.5 years, interferon-alfa therapy resulted in HBV DNA clearance in 35% of treated children, HBeAg clearance in 10%, and normalization of serum transaminase levels in 39% at treatment completion. Six to eighteen months after therapy discontinuation, 29% of children had persistent HBV DNA and 23% demonstrated HBeAg clearance. Children most likely to respond to interferon treatment are of younger age, higher baseline serum transaminase levels, and lower baseline HBV

DNA levels. Response is less likely (10%) in those with normal serum transaminase levels, high HBV DNA levels, HBV genotypes C or D, or those with HBeAg-negative chronic HBV infection. Interferon-alfa therapy might be considered for treatment of chronic hepatitis B in HIV-coinfected children who do not require antiretroviral therapy for treatment of their HIV infection **(BIII)**.

The standard course of interferon-alfa therapy for children without HIV infection is 24 weeks. Pegylated interferon-alfa, which results in more sustained plasma interferon concentrations and can be administered via injection once weekly for 48 weeks, has proven superior to standard interferon-alfa in the treatment of HBV-infected adults. However, the limited data on the use of pegylated interferon-alfa in children come from treatment of hepatitis C infection and appropriate dosing information is not available for use of pegylated interferon-alfa for treatment of chronic hepatitis B in children.

### Lamivudine

Lamivudine (3TC) is an oral nucleoside analogue that inhibits HBV replication. It is approved for use in children aged 2 to 17 years with compensated liver disease due to chronic hepatitis B. In a placebo-controlled trial in children with chronic hepatitis B without HIV infection, lamivudine was well tolerated, with virologic response (clearance of HBV DNA and HBeAg) seen in 23% of children receiving 52 weeks of lamivudine therapy, compared with 13% in placebo recipients. Response rates were higher (35%) for children with baseline serum transaminases >2 times normal. In a 2-year, open-label extension of this study, 213 children who remained HBeAg positive after 1 year of therapy were continued on lamivudine treatment; virologic response was seen in 21% of the original lamivudine recipients, compared with 30% of prior placebo recipients, indicating that additional clinical response could occur over time with prolonged treatment. However, longer duration of lamivudine therapy was also associated with progressive development of lamivudine-resistant HBV, with base pair substitutions at the tyrosine-methionine-aspartate-aspartate (YMDD) locus of HBV DNA polymerase. The incidence of YMDD mutations in the prior placebo group increased from 0% at baseline, to 19% at month 12, and 49% at month 24. In the prior lamivudine group, the incidence of YMDD mutations increased from 24% at baseline, to 59% at month 12, and 64% at month 24. Lower virologic response rates (5%) were seen at 24 months in patients with the YMDD variant, compared with 54% in patients with wild-type virus.

Accordingly, lamivudine should not be used as a single agent for treatment of chronic hepatitis B in HIV-infected children because of the risk of developing HIV resistance to lamivudine **(EIII)**; as discussed above, lamivudine should only be used in HIV/HBV-coinfected children in combination with other antiretroviral drugs in a HAART regimen **(BIII)**. It is important to note that the dose of lamivudine required to treat HIV infection is higher than to treat pediatric chronic hepatitis B alone; therefore, the higher dose of lamivudine should be used in HIV/HBV-coinfected children to avoid development of lamivudine-resistant HIV **(AIII)**. Lamivudine resistance should be suspected if HBV DNA levels increase during antiviral therapy. Such increases may precede increases in serum transaminase levels (hepatic flare) and liver decompensation.

### Emtricitabine

Emtricitabine is structurally similar to lamivudine and is active against HBV and HIV, although not approved for treatment of chronic hepatitis B. Like lamivudine, emtricitabine is also associated with a relatively rapid onset of HBV and HIV drug resistance, and patients with suspected lamivudine resistance should be assumed to have cross-resistance to emtricitabine. Lamivudine and emtricitabine should be considered interchangeable for treatment of chronic hepatitis B and not additive. As with lamivudine, emtricitabine should not be used for treatment of chronic hepatitis B in coinfecting children who are not being treated with combination antiretroviral therapy for their HIV infection due to the risk of developing HIV-associated resistance mutations **(EIII)**.

#### Adefovir

Adefovir dipivoxil is an oral nucleotide analogue active against HBV. Adefovir, although active against HBV, has minimal anti-HIV activity, and HIV resistance has not been observed to develop in patients receiving adefovir at this dose for 48 weeks. The development of HBV resistance to adefovir is much lower than with lamivudine, being reported as 2% after 2 years, 4% after 3 years, and 18% after 4 years of therapy in adults. These adefovir-associated mutations in HBV *PoI* gene result in only a modest (3- to 8-fold) increase in the 50% inhibitory concentration and are partially cross-resistant with tenofovir. Adefovir is now FDA approved for adults who require treatment for chronic hepatitis B but do not yet require treatment for their HIV infection. Adefovir has been studied in HIV/HBV-coinfecting adults with lamivudine-resistant HBV infection and virologic HBV suppression was demonstrated. Safety and effectiveness of adefovir for treatment of chronic hepatitis B in children has not yet been established; however, an ongoing randomized clinical trial is evaluating its use in HIV-uninfected children aged 2 to 17 years with chronic hepatitis B.

#### Tenofovir

Tenofovir is a nucleotide analog structurally similar to adefovir that has been shown to reduce HBV DNA levels in adult patients with lamivudine-resistant as well as wild-type HBV infection. Tenofovir is not approved for use in the treatment of chronic hepatitis B. However, a study in HIV/HBV-coinfecting adults receiving stable antiretroviral therapy comparing treatment with tenofovir or adefovir found similar efficacy in suppression of HBV DNA without differences in toxicity. Another study of HIV/HBV-coinfecting adults receiving tenofovir in addition to lamivudine as part of their antiretroviral regimen found that HBV DNA became undetectable in 30% of HBeAg-positive and 82% of HBeAg-negative patients, most of whom had lamivudine-resistant HBV infection. As noted earlier, tenofovir is not approved for use in HIV-infected children aged <18 years and there is no pediatric formulation. However, for HIV/HBV-coinfecting adolescents who require treatment of both infections and who can receive adult doses, tenofovir in combination with an anti-HBV nucleoside (either lamivudine or emtricitabine) can be considered for treatment **(BIII)**; a combined formulation of emtricitabine and tenofovir (Truvada) is available for adults. As with lamivudine and emtricitabine, tenofovir should not be used for treatment of chronic hepatitis B in HIV-coinfecting patients who are not receiving combination antiretroviral therapy for treatment of their HIV infection due to the risk of developing HIV-associated resistance mutations **(EIII)**.

### Entecavir

Entecavir is an oral nucleoside analogue that inhibits HBV DNA polymerase. Compared with lamivudine, entecavir therapy results in greater HBV viral suppression, increased normalization of serum transaminase levels, improved liver histology, and lower HBV resistance rates. HBV viral suppression has also been demonstrated in HIV/HBV-coinfected adults. Entecavir treatment is approved for treatment of chronic hepatitis B in adults and is preferred for lamivudine-resistant HBV infections. However, it was recently demonstrated to have suppressive activity against HIV. Entecavir should not be used in HIV/HBV-coinfected patients who are not receiving combination antiretroviral therapy for treatment of their HIV infection. There are no pediatric data on safety and efficacy of entecavir.

### Telbivudine

Telbivudine is a thymidine nucleoside analogue that was approved for the treatment of chronic hepatitis B in adults. It is well tolerated, but like lamivudine, there is emergence of resistance over time, and telbivudine is not active against lamivudine-resistant HBV. No data are currently available on telbivudine in HIV/HBV-coinfected adults. There are no pediatric data on safety and efficacy of telbivudine.

### Duration of Therapy

The optimal duration of therapy in HIV/HBV-coinfected children is not known. The duration of interferon-alfa treatment in HIV-uninfected children with chronic hepatitis B is 6 months. At least 1 year of lamivudine therapy is recommended for HIV-uninfected children with chronic hepatitis B, with continuation of medication for  $\geq 6$  months after documented HBeAg seroconversion. However, because lamivudine would only be given to HIV/HBV-coinfected children who need HIV treatment and as part of a suppressive antiretroviral regimen, treatment with lamivudine (or other anti-HBV drugs with anti-HIV activity) should be continued indefinitely in children with HIV/HBV coinfection, even in the setting of HBeAg seroconversion **(CIII)**.

### *Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome (IRIS)*

The parameters of successful therapy of chronic hepatitis B are not well defined, but markers of improvement would include decreased hepatic necroinflammatory disease, normalization of serum transaminase levels, reduction of HBV DNA levels, and HBeAg seroconversion. In children starting treatment for chronic hepatitis B, serum transaminase levels should be measured every 3 to 6 months. If the child is also initiating HAART, some experts would monitor transaminase levels more frequently in the first few months of therapy (e.g., monthly for 3 months) due to the risk of IRIS (see below). Monitoring of response to treatment for chronic hepatitis B is based on testing for HBV DNA and HBeAg and anti-HBe antibody on the same schedule as transaminase evaluations (every 3 to 6 months). Among persons who are HBeAg positive, treatment for chronic hepatitis B should be continued until HBeAg seroconversion has been achieved and  $\geq 6$  months of additional treatment has been completed after the appearance of anti-HBe. Close monitoring for relapse is needed after withdrawal of therapy. Among persons who

are HBeAg negative, treatment should be continued until HBsAg clearance has been achieved.

In HIV/HBV-coinfected persons starting HAART, serum transaminase elevations ("flares") may be seen as part of IRIS, or they may occur secondary to HAART-associated hepatotoxicity. HBV-associated liver injury is thought to be immune mediated, and restoration of immunocompetence with antiretroviral treatment may reactivate liver inflammation and damage. Initiation of HAART without anti-HBV therapy may lead to reactivation of HBV. This does not represent a failure of HAART therapy but rather a sign of immune reconstitution. IRIS is manifested by an increase in serum transaminase levels as the CD4 count increases during the first 6 to 12 weeks of HAART. Thus, serum transaminase levels should be monitored closely following introduction of HAART. In such situations, HAART should be continued and treatment for HBV initiated. The prognosis for most IRIS cases is favorable because a robust inflammatory response may predict an excellent response to HAART in terms of immune reconstitution and, perhaps, improved survival. It may be difficult in a patient experiencing a hepatic flare to differentiate between IRIS and drug-induced liver toxicity, and there is no reliable clinical or laboratory predictor to distinguish between the two. Close interaction of the HIV specialist with a specialist in hepatic disease is recommended in such patients; prompt consultation with a hepatologist should be sought if elevated aminotransferases are associated with clinical jaundice or other evidence of liver dysfunction (e.g., low serum albumin).

Clinical and laboratory exacerbations of hepatitis and hepatic flare may occur in children receiving HAART should agents with anti-HBV activity be discontinued. Some experts recommend that once antiretroviral drugs with anti-HBV activity are begun, they should be continued unless contraindicated or until the child has been treated for >6 months after HBeAg seroconversion and can be closely monitored on discontinuation **(BIII)**. If discontinuation of therapy for chronic hepatitis B results in a hepatic flare, therapy for chronic hepatitis B should be reinstituted **(BIII)**.

Some clinicians recommend monitoring HBV-infected children or adolescents for HCC development with baseline screening and then yearly determinations of serum alpha fetoprotein (AFP) levels and abdominal ultrasonography, although there are no data to supporting the benefit of such surveillance.

Although adverse effects of interferon-alfa use in children, while frequent, are usually not severe or permanent, approximately 5% of children require treatment discontinuation. The most common side effects include an influenza-like syndrome, cytopenias, and neuropsychiatric effects. Influenza-like symptoms consisting of fever, chills, headache, myalgias, arthralgias, abdominal pain, nausea, and vomiting are seen in 80% of patients during the first month of treatment. The incidence of these side effects decreases substantially during the first 4 months of therapy; premedication with acetaminophen or ibuprofen might reduce the incidence of side effects. Subtle personality changes have been reported in 42% of children that resolve when therapy is discontinued. Depression and suicidal ideation have also been reported in clinical trials of children treated with interferon-alfa. Neutropenia, which resolves after discontinuation of therapy, is the most common laboratory abnormality; anemia and thrombocytopenia are less common. Abnormalities in thyroid function (hypo- or hyperthyroidism) have

been reported with interferon-alfa therapy. Loss of appetite with transient weight loss and impairment in height growth may occur, but usually resolves after completion of therapy. Less commonly observed side effects of interferon-alfa include epistaxis and transient mild alopecia. The presence of antinuclear autoantibodies has been detected in some children treated with interferon-alfa. Interferon-alfa therapy is contraindicated for children with decompensated liver disease; severe cytopenias; severe renal, cardiac, or neuropsychiatric disorders; and autoimmune disease **(EII)**. Elevation of serum transaminase levels has been reported during interferon-alfa therapy in children and adults but is not generally an indication to stop therapy; these flares may herald impending HBeAg seroconversion. Children receiving interferon-alfa therapy should be monitored with a complete blood count and serum thyroid stimulating hormone (TSH) level at baseline and periodically (e.g., at least every 3 months) for the duration of treatment.

Lamivudine is generally well tolerated in children; rare cases of lactic acidosis and pancreatitis have been reported in HIV/HBV-coinfected adults. Tenofovir and adefovir can cause renal tubular disease. Patients receiving either drug should have baseline urinalysis and periodic serum creatinine and phosphate monitoring. Administration of other nephrotoxic agents increases the risk of renal toxicity.

#### *Management of Treatment Failure*

Treatment failure is defined as the presence of ongoing HBV replication, persistent serum transaminase elevations, and the failure of HBeAg seroconversion in those who are HBeAg positive. Flares of liver disease with increasing HBV DNA levels can be seen with the development of resistance to lamivudine or emtricitabine.

For children who have received initial treatment for chronic hepatitis B with standard dose interferon-alfa monotherapy, use of higher dose interferon-alfa for retreatment has been found to result in improved response in some children **(CII)**. Lamivudine has also been used as secondary therapy for children without HIV infection who have not responded to standard interferon-alfa therapy **(CII)**; in HIV-infected children, initiation of a lamivudine-based HAART regimen could be considered **(CIII)**.

For HIV/HBV-coinfected children developing lamivudine resistance during therapy, treatment options are more limited because of the lack of pediatric data on adefovir, entecavir, and tenofovir. Because these HBV drug-resistant isolates may have lower replicative capacity than wild-type HBV, some experts recommend continuation of lamivudine or emtricitabine therapy in such cases. Alternatively, the addition of interferon-alfa therapy could be considered or, in children old enough to receive adult doses of tenofovir or adefovir, addition of tenofovir or adefovir to the regimen could be considered **(CIII)**.

#### **Prevention of Recurrence**

Not applicable.

#### *Discontinuing Secondary Prophylaxis*

Not applicable.

## **Viral Infections: Hepatitis C Virus (HCV)**

### **Prevention Recommendations**

#### *Prevention of Exposure*

All HIV-infected individuals, including HIV-infected pregnant women, should be screened for HCV. There is currently no reliable strategy to prevent perinatal HCV transmission. Cesarean delivery is not associated with reduced perinatal transmission of HCV infection and is not recommended for this purpose for women with chronic HCV infection who are HIV uninfected. Scheduled cesarean delivery is recommended for HIV-infected women with HIV RNA levels >1,000 copies/mL near the time of delivery to prevent perinatal HIV transmission. The limited data available suggest that breastfeeding does not transmit HCV. However, to prevent HIV transmission in the United States, where safe infant formula is available, it is recommended that HIV-infected women should not breastfeed.

There are currently no vaccines available to prevent HCV infection.

Adolescents considering tattooing or body-piercing should be informed of potential risks for acquiring HCV, which could be transmitted if equipment is not sterile or if proper infection control procedures are not followed, and to avoid injection drug use and unprotected sex. HCV-infected persons should be advised not to share toothbrushes, razors, and other personal care articles that might be contaminated with blood to prevent transmission of HCV to others.

#### *Preventing First Episode of Disease*

Patients with chronic liver disease can develop fulminant hepatitis from hepatitis A or B infection; all children (regardless of HIV and HCV infection status) should receive standard immunization with hepatitis A and B vaccines **(AIII)**.

### **Treatment Recommendations**

#### *Treatment of Disease*

There are a limited number of published studies on treatment of HCV-infected children from which to make treatment recommendations. Pediatric trials that are currently under way in the United States, including the PEDS-C study, a randomized, double-blind, placebo-controlled trial of pegylated interferon-alfa with and without ribavirin, should provide additional data in the future. Data on treatment of children coinfecting with HCV and HIV are even more limited. Consultation with providers with expertise in treating chronic pediatric HCV infection is recommended.

#### HIV/HCV-Coinfected Adults and Adolescents

Current guidelines suggest that treatment be considered in any nonpregnant HCV-infected adult with abnormal serum transaminase levels with a liver biopsy

showing chronic hepatitis with significant fibrosis and compensated liver disease. Treatment should be considered for those for whom potential benefits of treatment are judged to outweigh potential risks, including those infected with HCV genotype 2 or 3, those with stable HIV infection not requiring antiretroviral therapy, and those with cryoglobulinemic vasculitis or glomerulonephritis. Baseline serum HCV ribonucleic acid (RNA) level and HCV genotype are the primary predictors of response to treatment; younger age, higher CD4 count, elevated transaminase levels, lack of liver fibrosis, low body mass index, lack of insulin resistance, and white race are some other variables associated with better treatment response. The recommended treatment is combined pegylated-interferon-alfa-2a or-2b plus daily oral ribavirin for 48 weeks regardless of HCV genotype. In HIV/HCV-coinfected adults, sustained virologic response (SVR) rates range from 44% to 73% for treatment of HCV genotype 2 and 3 infection, and 14%–29% for HCV genotype 1 infection. Although some data from clinical treatment trials reported at recent conferences suggest better SVR rates, these may be due to better preselection of patients for therapy or improved adherence following dose adjustment(s). Improved response to anti-HCV treatment is seen in HIV-infected adults with CD4 count  $>200$  cells/mm<sup>3</sup>, and therefore HAART should be considered prior to the initiation of anti-HCV therapy in HIV-infected patients with CD4 count  $<200$  cells/mm<sup>3</sup>. Anti-HCV treatment is not generally recommended during pregnancy for HCV-infected women because ribavirin is teratogenic.

#### HCV-Infected Children without HIV Infection

Treatment of HIV-uninfected children with HCV infection aged  $<3$  years is generally not recommended as spontaneous HCV clearance may occur in this age group (**DIII**). All decisions regarding treatment of HCV infection in children should be individualized since HCV generally causes mild disease in children and there are few data to identify risk factors that differentiate those at greater risk of progression of liver disease.

The only currently FDA-approved therapy for HCV-infected children between the ages of 3 and 17 years with compensated liver disease is combined standard interferon-alfa-2b and ribavirin. Standard interferon-alfa is given by subcutaneous injection three times per week. Ribavirin oral solution has been approved for treatment of chronic HCV infection among children aged  $\geq 3$  years. For HIV-uninfected children with HCV infection, a 24-week course of therapy is recommended for genotypes 2 and 3; 48-week courses are given for other HCV genotypes. Combination therapy with standard interferon-alfa and ribavirin results in overall SVR rates ranging from 46% to 65% and is well tolerated in children. Similar to data from adults, children infected with genotype 1 were less likely to have an SVR (36% compared with 84% of those infected with genotype 2 or 3). Other factors associated with favorable response to anti-HCV treatment in children include lower pretreatment HCV RNA levels, white race, and possibly younger age.

#### HIV/HCV-Coinfected Children

There are no specific treatment studies of children with HIV/HCV-coinfection and recommendations are primarily based on adult data. Since therapy for HCV infection is more likely to be effective in younger patients and in those without advanced disease or immunodeficiency, treatment should be considered for all

HIV/HCV-coinfected individuals, including HIV-infected children age >3 years in whom there are no contraindications to treatment **(BIII)**. Some specialists would treat children infected with HCV genotypes 2 or 3 without first obtaining a liver biopsy. Pegylated interferon-alfa, which is administered via injection once weekly for 48 weeks combined with ribavirin, is recommended for treatment of HCV infection in adults. However, pegylated interferon-alfa is not currently FDA approved for use in HCV-infected children, although it is under study. Based on the increased efficacy of combination therapy with ribavirin and either standard or pegylated interferon-alfa and data from adults, treatment of HCV-infected children, regardless of HIV status, should include combination therapy with ribavirin and interferon-alfa **(BIII)**. In HIV/HCV-coinfected adults, the recommended duration of treatment is 48 weeks for infections with all HCV genotypes, including 2 and 3, because coinfecting adults may not respond as well as those without HIV infection and may have greater relapse rates. Moreover, the efficacy of shorter treatment duration has not been adequately evaluated in HIV-infected persons. By extrapolation, 48 weeks of therapy are also recommended for HIV/HCV-coinfected children **(BIII)**. The concomitant use of antiretroviral therapy and anti-HCV therapy is complicated by potential drug interactions. Ribavirin enhances phosphorylation of didanosine, which could increase the risk of toxicity; therefore, these drugs should not be used together **(EI)**. Ribavirin and zidovudine both are associated with anemia and when possible should not be administered together **(DII)**.

#### *Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome*

Although there are no evidence-based long-term monitoring guidelines for children with perinatally acquired HCV, many experts monitor HCV RNA levels and serum transaminase levels every 6 to 12 months and hemogram and serum alpha-fetoprotein (AFP) levels annually. Serum transaminase levels can fluctuate and do not necessarily correlate with histologic liver damage, as significant liver disease can be present in patients with normal serum transaminase levels. In HCV-infected persons without HIV, HCC is rarely seen in the absence of cirrhosis. The benefit of serum AFP and abdominal sonography as screening tools for HCC have not been studied in children. Some experts will perform periodic sonographic screening at defined intervals (every 2 to 5 years) in children with chronic HCV infection, whereas other experts will do these tests only in those with advanced liver disease and/or rising serum AFP concentrations. The risk for development of HCC in HCV-infected children, with or without HIV infection, is not known.

HCV RNA quantitation is used to monitor response to antiviral therapy. HCV RNA levels should be performed at baseline, after 12 and 24 weeks of antiviral therapy, at the time of treatment completion (48 weeks), and 6 months after treatment cessation. Some experts will continue to perform serial HCV RNA testing at 6- to 12-month intervals for an additional 1 to 5 years to exclude late virologic relapse. Decreases in HCV RNA  $\geq 2$  logs below the baseline during the first 12 weeks of therapy constitute an early virologic response (EVR). An SVR is defined as the absence of detectable HCV RNA using an HCV RNA assay with a lower limit of detection of  $\geq 50$  IU/mL at 24 weeks after the end of antiviral treatment. Relapse is defined as HCV RNA rebound at the end of therapy following an initial response to undetectable HCV RNA levels. Nonresponse is defined as the failure to suppress HCV RNA below detection at any time during treatment,

whereas breakthrough is the re-emergence of detectable HCV RNA following suppression below the limits of detection despite the continuation of therapy.

In the absence of data from HIV/HCV-coinfected children, the same criteria should be used for determining response to therapy as in HIV/HCV-coinfected adults. If an EVR is observed after the first 12 weeks of treatment, completion of additional HCV therapy is recommended. Adult patients who fail to achieve an EVR by week 12 have a limited chance (<3%) of achieving SVR regardless of duration of therapy, and treatment may be discontinued after 12 weeks in such patients. Persons who achieve a  $\geq 2 \log_{10}$  reduction in HCV RNA level but remain HCV RNA detectable after 12 weeks of therapy should be retested after the completion of 24 weeks of therapy. If HCV RNA remains detectable after 24 weeks, anti-HCV treatment should then be stopped, whereas an additional 24 weeks of therapy is indicated (total 48 weeks) if HCV RNA is not detected at that time. Persons who achieve an undetectable HCV RNA level after 12 weeks of therapy should complete an additional 36 weeks of anti-HCV treatment (total 48 weeks).

In addition to HCV RNA quantitation, patients receiving antiviral therapy for HCV infection should be closely monitored for medication side effects with complete blood count, serum transaminase levels, and tests of thyroid function. If the child is also initiating HAART, some experts would monitor transaminase levels more frequently in the first few months of therapy (e.g., monthly for 3 months) due to the risk of IRIS (see below).

Side effects of interferon-alfa in children, while frequent, are usually not severe; approximately 5% of children require treatment discontinuation. The most common side effects include influenza-like symptoms consisting of fever, chills, headache, myalgias, arthralgias, abdominal pain, nausea, and vomiting, seen in 80% of patients during the first month of treatment. However, these symptoms usually resolve over time and are usually not treatment limiting; premedication with acetaminophen or ibuprofen might reduce the incidence of side effects. Subtle personality changes that resolve when therapy is discontinued have been reported in 42% of children. Depression and suicidal ideation have also been reported in clinical trials of children treated with interferon-alfa. Neutropenia, which resolves after discontinuation of therapy, is the most common laboratory abnormality; anemia and thrombocytopenia are less common. Abnormalities in thyroid function (hypo- or hyperthyroidism) have been reported with interferon-alfa therapy. Loss of appetite with transient weight loss and impairment in height growth may occur, but usually resolves after completion of therapy. Less commonly observed side effects of interferon-alfa include epistaxis and transient mild alopecia. Certain children have experienced antinuclear autoantibodies. Interferon-alfa therapy is contraindicated for children with decompensated liver disease; substantial cytopenias; severe renal, cardiac, or neuropsychiatric disorders; and autoimmune disease **(EII)**.

Side effects of ribavirin include hemolytic anemia and lymphopenia. Ribavirin-induced hemolytic anemia is dose dependent and usually presents with a substantial decrease in hemoglobin within 1 to 2 weeks of ribavirin initiation, but the trend usually stabilizes. Significant anemia (hemoglobin <10 gm/dL) occurs in only about 10% of ribavirin-treated children. Use of erythropoietin for the management of clinically significant anemia during HCV treatment can be considered. Coadministration of didanosine is contraindicated in children receiving

ribavirin, since this combination may increase the risk of mitochondrial toxicity and hepatic decompensation. Children receiving concomitant zidovudine may be more likely to experience bone marrow suppression, and if possible, zidovudine should be avoided in children receiving ribavirin. If zidovudine and ribavirin are given together, the child should be closely monitored for neutropenia and anemia. Ribavirin is teratogenic and should not be used in pregnant women. Sexually active female and male adolescents or those likely to become sexually active who are receiving ribavirin should be counseled about the risks and need for consistent contraceptive use during and for 6 months after completion of ribavirin therapy.

As with HIV/HBV coinfection, the institution of HAART therapy in HIV/HCV-coinfected patients may result in worsening hepatitis, with increases in serum transaminase levels and clinical signs of liver disease including hepatomegaly and jaundice. This does not represent a failure of HAART therapy but rather a sign of immune reconstitution. IRIS is manifested by an increase in serum transaminase levels as the CD4 count increases during the first 6 to 12 weeks of HAART. Thus, serum transaminase levels should be monitored closely following introduction of HAART in HIV/HCV-coinfected children. The prognosis for most IRIS cases is favorable because a robust inflammatory response may predict an excellent response to HAART in terms of immune reconstitution and, perhaps, improved survival. It may be difficult in a patient experiencing a hepatic flare to differentiate between IRIS and drug-induced liver toxicity, and there is no reliable clinical or laboratory predictor to distinguish between the two. Close interaction of the HIV specialist with a specialist in hepatic disease is recommended in such patients; prompt consultation with a hepatologist should be sought if elevated aminotransferases are associated with clinical jaundice or other evidence of liver dysfunction (e.g., low serum albumin).

#### *Management of Treatment Failure*

There are no data on which to base recommendations for treatment of HIV/HCV-coinfected children or adults who fail to respond to initial HCV treatment. In HIV/HCV-coinfected adults, a second course of treatment for nonresponders (those who fail to achieve EVR by week 12 or undetectable HCV load at week 24) or patients who relapse has limited chances of resulting in SVR. Therapeutic interventions for such patients need to be individualized based on the prior response, tolerance, and adherence to therapy; severity of liver disease; viral genotype; and other underlying factors that might influence response. Some experts might extend the duration of treatment (e.g., 72 weeks) in adult patients who experience a virologic response followed by relapse after adequate HCV therapy, or for patients with advanced fibrosis, long-term administration of low-dose pegylated interferon. No data exist in HIV/HCV-coinfected children on which to base a recommendation.

#### **Prevention of Recurrence**

Not applicable.

#### *Discontinuing Secondary Prophylaxis*

Not applicable.

## **Viral Infections: Human Herpesvirus 6 and 7 (HHV-6 and HHV-7)**

### **Prevention Recommendations**

#### *Preventing Exposure*

As HHV-6 and HHV-7 infections are ubiquitous, prevention of primary infection is not possible. Among transplant recipients, prophylactic ganciclovir may decrease the number of episodes and severity of HHV-6 reactivation.

#### *Preventing First Episode of Disease*

Given the ubiquity of HHV-6 and -7 during early childhood and the lack of an effective vaccine, prevention of HHV-6 disease is not feasible.

#### *Discontinuing Primary Prophylaxis*

Not applicable.

### **Treatment Recommendations**

#### *Treatment of Disease*

The majority of HHV-6 primary infections result in a mild, self-limited, febrile illness. For the immunodeficient adult or child with possible HHV-6-associated lung or CNS disease, care must be used to exclude other diagnostic possibilities. There are no clear indications for treatment of HHV-6 infection in HIV-infected children, although treatment might be considered for the rare instance of severe encephalitis proven to be due to HHV-6. However, there are no clinical trials or proven therapies for HHV-6. Based on data in adults, the drugs that might be considered for severe HHV-6 disease are ganciclovir, foscarnet, and cidofovir. However, although *in vitro* data suggest ganciclovir and foscarnet are active against HHV-6, there are only limited data to support their use among HIV-infected patients with possible HHV-6 related illness **(CIII)**. Ganciclovir has been used for treatment of HHV-6 encephalitis in adult transplant patients. However, limited success of ganciclovir therapy in preventing fatal outcome has been reported; in the patients who experienced a fatal outcome, ganciclovir did not achieve a reduction of HHV-6 load in cerebrospinal fluid (CSF). Case reports have documented both successful and disappointing results of foscarnet treatment for HHV-6 encephalitis in transplant recipients. Cidofovir followed by foscarnet has been used in a stem cell transplant recipient who developed HHV-6 encephalitis with evidence of a significant reduction in HHV-6 load in CSF and in plasma after cidofovir administration. There has been one case report of successful use of high-dose ganciclovir to treat HHV-6 encephalitis in a pediatric bone marrow transplant patient. Given the lack of data in children, no specific recommendations can be made.

HHV-7 has not been recognized as being responsible for any specific disease in HIV-infected individuals and no treatment is indicated.

### *Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome*

The major side effect of ganciclovir is myelosuppression (i.e., anemia, neutropenia, and thrombocytopenia). Dose reduction or interruption due to hematologic toxicity may be necessary in  $\leq 40\%$  of patients receiving intravenous ganciclovir; granulocyte colony-stimulating factor can be used to ameliorate marrow suppression. The main toxicities of foscarnet are decreased renal function and metabolic derangements. For patients receiving ganciclovir or foscarnet, monitoring of complete blood counts, serum electrolytes, and renal function should be performed twice weekly during induction therapy and once weekly thereafter. The major side effect of cidofovir is potentially irreversible nephrotoxicity; the drug produces proximal tubular dysfunction including Fanconi syndrome and acute renal failure. When present, renal toxicity manifests as proteinuria and glycosuria. To minimize nephrotoxicity, probenecid should be administered before each infusion and intravenous hydration with normal saline should be administered before and after each cidofovir infusion. For patients receiving intravenous cidofovir, blood urea nitrogen, creatinine, and urinalysis should be performed before each infusion; administration of the drug is contraindicated if renal dysfunction or proteinuria is detected. Other reported adverse events include anterior uveitis and ocular hypotony; serial ophthalmologic monitoring for anterior segment inflammation and intraocular pressure is needed while receiving the drug systemically. Cidofovir should not be administered concomitantly with other nephrotoxic agents. Cidofovir therapy must be discontinued if serum creatinine increases  $\geq 0.5$  mg/dL above baseline.

HHV-6 and -7 have not been shown to be demonstrated to be associated with IRIS with HAART treatment in HIV-infected children or adults.

### *Management of Treatment Failure*

Mutations conferring resistance of HHV-6 to ganciclovir, cidofovir, and foscarnet have been described. It is unknown if a change from one drug to the other would be beneficial.

### **Prevention of Recurrence**

No data exist on prevention of HHV-6 or HHV-7 reactivation from latency in HIV-infected patients.

### *Discontinuing Secondary Prophylaxis*

Not applicable.

## **Viral Infections: Human Herpesvirus-8 (HHV-8) Disease**

### **Prevention Recommendations**

#### *Preventing Exposure*

For HIV-infected individuals, coinfection with HHV-8 places them at risk for Kaposi's sarcoma (KS). The risk is highest in adults (compared to children) and for those with severe immunodeficiency. As routine testing of children and adults for HHV-8 is not recommended, the serostatus of newly identified HIV-infected individuals is generally not known. For adolescents diagnosed with KS, counseling should include the possibility of the transmission of HHV-8 to their sexual contacts through intercourse and possibly kissing. Although efficacy of condom use for preventing HHV-8 exposure has not been established, HIV-infected persons should use latex condoms during every act of sexual intercourse to reduce exposure to sexually transmitted pathogens. HIV-infected injection drug users should be counseled not to share drug-injection equipment, even if both users are already HIV-infected, because of the chance of becoming infected with HHV-8 or other bloodborne pathogens.

In the future, HHV-8 testing of donated blood products prior to use for immunodeficient patients might be considered. In addition, the routine use of leukocyte reduction for red cell transfusions may lower the transmission risk.

Infants may acquire HHV-8 perinatally or through contact with infected family members and playmates. There is no effective way known to intervene to prevent childhood acquisition of HHV-8.

#### *Preventing First Episode of Disease*

The use of HAART with suppression of HIV replication has led to a marked decrease in the incidence of KS among HIV-infected adults and should be the goal of treatment wherever possible **(BII)**. Routine testing to identify HHV-8-seropositive HIV-infected individuals is not recommended at this time **(DIII)**. Although several antiviral agents inhibit HHV-8 replication *in vitro* (e.g., ganciclovir, foscarnet, cidofovir) there are no data on their use to prevent KS in HIV/HHV-8-coinfected individuals.

### **Treatment Recommendations**

#### *Treatment of Disease*

As the HIV-related clinical entities associated with HHV-8, such as KS and Castleman's disease, are oncologic in nature and traditionally have been treated with cytotoxic chemotherapy, specific treatment is not included in this report. However, effective suppression of HIV replication with HAART among HIV-infected patients with KS might prevent progression or occurrence of new lesions and should be considered for all persons with evidence of active KS and other HHV-8-associated malignant lymphoproliferative disorders **(BII)**.

In HIV-infected adults, HHV-8 cellular viremia and higher viral load have been associated with disease progression. The use of specific antiviral agents, such as ganciclovir, foscarnet, and cidofovir, which have *in vitro* activity against the lytic but not latent phase of HHV-8, to treat has not been widely studied. Additionally, the vast majority of infected cells are not undergoing lytic replication and antiherpes medications have had little or no effect on established KS or HHV-8 cellular viremia. Efforts to induce lytic replication or to attack the episomal (latent) HHV-8 genome are in progress.

In contrast to KS, many of the cells in Castleman's disease support lytic replication of HHV-8, and treatment of Castleman's disease with antiherpesvirus drugs has led to substantial clinical improvement in some studies. The use of intravenous ganciclovir or oral valganciclovir is recommended for the treatment of multicentric Castleman's disease **(BII)** and may be a useful adjunctive therapy in the treatment of primary effusion lymphoma **(BII)**. Appropriate chemotherapy, in combination with potent antiretroviral therapy, should be considered for patients with visceral KS or primary effusion lymphoma **(BII)**.

#### *Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome*

There have been reports of rapid progression of KS following initiation of HAART and following a change from a failing regimen to a more potent one. Progression of KS, representing IRIS, generally appeared within 8 weeks of starting a potent HAART regimen. Most patients experienced a rapid progression of cutaneous lesions, although there are several reports of sudden worsening of pulmonary KS, with resultant deaths in at least four patients. All reported fatalities were linked to pulmonary KS. In most cases, HAART was continued with stabilization and then regression of lesions. In more severe cases, especially those involving visceral lesions, chemotherapy was instituted and, in combination with HAART, led to regression of the KS.

#### **Prevention of Recurrence**

Effective suppression of HIV replication with HAART among HIV-infected patients with KS might prevent KS progression or occurrence of new lesions and should be considered for all persons with evidence of active KS **(BII)**.

#### *Discontinuing Secondary Prophylaxis*

Not applicable.

#### **Viral Infections: Herpes Simplex Virus (HSV)**

##### **Prevention Recommendations**

##### *Preventing Exposure*

The rate of HSV transmission to the fetus and neonate among HIV-infected pregnant women coinfecting with HSV is not known. Although isolated cases of *in utero* HSV transmission with primary infection during pregnancy among HIV-uninfected women have been reported, the predominant risk, regardless of HIV coinfection, is from maternal genital shedding at delivery. Effective HAART regimens may decrease, but not prevent, the frequency of maternal genital HSV shedding and recurrence of genital lesions.

Use of acyclovir or valacyclovir in late pregnancy suppresses genital herpes outbreaks and shedding in late pregnancy among HIV-uninfected women with HSV infection and appears to reduce the need for cesarean delivery for recurrent HSV. However, the safety and efficacy of this strategy have not been evaluated

among HIV-infected women who are more likely to have antibody to HSV-2 and to have both symptomatic and asymptomatic reactivation of genital HSV. Therefore, the use of acyclovir or valacyclovir specifically to reduce the need for cesarean delivery among HIV/HSV-coinfected women is not recommended **(DIII)**. In addition, there are case reports of HSV-infected neonates born to women who received suppressive antiviral therapy near term.

For pregnant women with active genital HSV at the onset of labor, delivery by elective cesarean section, preferably prior to rupture of membranes, is recommended **(AI)**.

For the HIV-infected child, exposure to HSV-1 is an inevitable part of childhood, and there are no proven ways of preventing exposure. Direct contact of children with secretions from active HSV lesions (such as herpes labialis) on the mother, household, or other individuals should be avoided.

Among sexually active, HIV-infected adults, latex condoms should be used during every act of sexual intercourse to reduce the risk for exposure to HSV and to other sexually transmitted pathogens **(AII)**. They should specifically avoid sexual contact when herpetic lesions (genital or orolabial) are evident **(AII)**. There are data to suggest that chronic suppressive therapy with valacyclovir in persons with genital herpes reduced HSV-2 transmission to susceptible heterosexual partners by 50%. In HIV-infected adults, HAART was found to reduce the frequency of symptomatic herpetic lesions compared to adults not on HAART, but mucosal HSV-2 shedding was similar.

#### *Preventing First Episode of Disease*

Antiviral prophylaxis after exposure to HSV or to prevent initial episodes of HSV disease among persons with latent infection is not recommended **(DIII)**.

### **Treatment Recommendations**

#### *Treatment of Disease*

Acyclovir is the drug of choice for treatment of local and disseminated HSV among infants and children, regardless of HIV-infection status **(AI)**. Both oral and intravenous preparations are available. Neonatal HSV disease should be treated with high-dose intravenous acyclovir (20 mg/kg/dose three times daily) administered for 21 days for CNS and disseminated disease and for 14 days for skin, eyes, and mouth (SEM) disease **(AI)**. Acyclovir therapy should not be discontinued in neonates with CNS disease unless a repeat CSF HSV DNA polymerase chain reaction (PCR) assay is negative near the end of treatment **(BIII)**. Orolabial lesions in HIV-infected children can be treated with oral acyclovir for 5 to 10 days **(AI)**. Moderate-to-severe mucocutaneous HSV lesions are best treated initially with intravenous acyclovir **(AI)**. Patients may be switched to oral therapy after the lesions have begun to regress, and therapy continued until lesions have completely healed. Acyclovir is the drug of choice for disseminated HSV and HSV encephalitis in children. Regardless of age, HSV encephalitis should be treated for 21 days **(AII)**. Genital HSV should be treated with oral acyclovir for 5 to 14 days **(AI)**. Trifluridine, a fluorinated pyrimidine nucleoside, is the treatment of choice for herpes keratoconjunctivitis, one drop

onto the cornea every 2 hours, not to exceed nine drops/day; it is not recommended for longer than 21 days **(AII)**.

Alternatives to acyclovir in older adolescents and adults include valacyclovir and famciclovir **(AI)**. Valacyclovir is a prodrug of acyclovir with improved bioavailability that is rapidly converted to acyclovir after absorption. Data are limited on valacyclovir in children; bioavailability is about 45% and independent of age in children. Based on limited available data, pediatric blood levels of acyclovir (from the prodrug valacyclovir) similar to levels achieved with valacyclovir tablets in adults can be achieved by administering an oral dose of valacyclovir of 20 – 25 mg/kg/dose given two to three times a day. However, no pediatric formulation is available, and hence this drug is an alternative only for children old enough to swallow the large valacyclovir tablets. Although tablets can be crushed, they have a very unpleasant taste. There are no specific data on the pharmacokinetics and dosing of famciclovir in children and no pediatric preparation is available.

#### *Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome*

Acyclovir is primarily excreted by the kidney; as a result, dose adjustment based on creatinine clearance is needed in patients with renal insufficiency or renal failure. Primary toxicities of acyclovir are phlebitis, renal toxicity, nausea, vomiting, and rash. Toxicities are similar for valacyclovir. In infants receiving high-dose acyclovir for neonatal disease, the major toxicity was neutropenia (e.g., absolute neutrophil count  $<1,000/\text{mm}^3$ ). Grade 3 or higher nephrotoxicity was observed in 6%. For children receiving high-dose IV acyclovir, monitoring of complete blood counts and renal function is recommended at initiation of treatment and once or twice weekly for the duration of treatment, particularly for those with underlying renal dysfunction or those receiving prolonged therapy.

Management of acyclovir-resistant herpes with foscarnet is associated with decreased renal function;  $\leq 30\%$  of patients experience increases in serum creatinine levels. Renal toxicity and foscarnet binding to divalent metal ions such as calcium lead to metabolic abnormalities in approximately one-third of patients, and serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures or cardiac dysrhythmias can occur. Abnormal liver transaminases and CNS symptoms also can occur. For patients receiving foscarnet, monitoring of complete blood counts and serum electrolytes and renal function should be performed twice weekly during induction therapy and once weekly thereafter **(AIII)**.

Atypical lesions that may have a delayed response to therapy have been reported in adults initiating HAART and attributed to IRIS.

#### *Management of Treatment Failure*

Treatment failure related to resistance to antiviral drugs should be suspected if lesions do not indicate signs of resolution within 7 to 10 days after initiation of therapy. Among immunocompromised patients with suspected acyclovir-resistant HSV, a lesion culture should be obtained and, if virus is isolated, susceptibility testing performed to confirm drug resistance.

The treatment of choice for acyclovir-resistant HSV is intravenous foscarnet **(AI)**. All acyclovir-resistant HSV strains are resistant to valacyclovir and most are resistant to famciclovir. Topical trifluridine or cidofovir also have been used successfully for lesions on cutaneous surfaces, although prolonged application for 21 to 28 days or longer might be required. Intravenous cidofovir has been used to treat a child with acyclovir- and foscarnet-resistant HSV.

### **Prevention of Recurrence**

Following neonatal HSV infection, administration of oral acyclovir prevented cutaneous recurrences of HSV after neonatal skin, eyes, and mouth (SEM) disease, but the effect of such therapy on neurologic outcome needs assessment, and additional investigation is necessary before routine use of suppressive therapy in this population can be recommended.

Because episodes of HSV disease can be treated successfully, chronic therapy with acyclovir is not required after lesions resolve. However, children who have frequent or severe recurrences (e.g., >3 to 6 severe episodes a year) can be administered daily suppressive therapy with oral acyclovir **(AI)**. Valacyclovir or famciclovir also are options for older children **(AI)**. Effective HAART therapy may also lessen the frequency of recurrences.

#### *Discontinuing Secondary Prophylaxis*

Not applicable, secondary prophylaxis not generally recommended in children.

### **Viral Infections: Human Papillomavirus (HPV)**

#### **Prevention Recommendations**

##### *Preventing Exposure*

HIV-infected persons should use latex condoms during every act of sexual intercourse to reduce the risk for exposure to sexually transmitted pathogens **(AII)**, including HPV.

##### HPV Vaccine

In June 2006, the FDA approved the first preventive vaccine for HPV types 16, 18, 6, and 11. HPV 16 and 18 cause almost 70% of invasive cervical cancers and HPV 6 and 11 cause 90% of external genital warts. HPV exposure is extremely common after sexual contact, not just sexual intercourse, is initiated. Administration of the vaccine is critical before the onset of sexual activity for it to be fully effective. Data for women without HIV infection showed efficacy rates of 95% for preventing HPV infection and high-grade cervical intraepithelial neoplasia (CIN) related to vaccine-related HPV strains and 99% efficacy for genital warts. However, if there was documented previous exposure to the vaccine HPV types, no efficacy was noted for that type, underscoring the fact that the vaccine is not therapeutic. A second vaccine targeting HPV 16 and 18 has had similar efficacy (Cervarix, GSK) and is expected to receive FDA approval in 2008.

Although considered safe, studies in HIV-infected persons are not yet available, so immunogenicity and efficacy in this population have not yet been established. However, because quadrivalent HPV vaccine is a noninfectious vaccine, it can be administered to females who are immunosuppressed as a result of disease or medications, including HIV-infected females. However, the immune response and vaccine efficacy might be less than that in persons who are immunocompetent (Figure 2 in the original guideline document). Studies of the immunogenicity of HPV vaccine are ongoing in HIV-infected females. Current CDC recommendations for HPV immunization for all children and adolescents should be followed for HIV-infected as well as uninfected individuals. The first dose of the HPV vaccine series should be administered to females aged 11 to 12 years but can be administered as early as 9 years. The second dose should be administered 2 months after the first dose and the third dose should be administered 6 months after the first dose. HIV-infected females aged 13 to 18 years who have not been previously vaccinated should also be vaccinated with the three-dose HPV vaccine series.

The HPV vaccine has not been shown to have any therapeutic benefit to treat existing HPV-related lesions in either HIV-infected or -uninfected women. There are no published studies using the HPV vaccine to prevent HPV infection and associated lesions of the anus, penis, or oral cavity in men and the vaccine is not currently approved for use in men in the United States. As in HIV-infected women there are no data on the safety or efficacy of the HPV vaccine in HIV-infected men.

#### *Preventing First Episode of Disease*

##### HPV-Associated Genital Epithelial Cancers among HIV-Infected Women

After a complete history of previous cervical disease has been obtained, HIV-infected sexually active women should have a pelvic examination and a cervical cancer screening test (Pap test, either conventional or liquid based). In accordance with the recommendation of the Agency for Health Care Policy and Research, the Pap smear should be obtained twice during the first year after diagnosis of HIV infection and, if the results are normal, annually thereafter **(AII)**. If the results of the Pap smear are abnormal, care should be provided according to treatment guidelines described for adolescents below. Adult women (e.g., aged >20 years) should be managed according to adult guidelines. No data are available to demonstrate that these guidelines to prevent cervical disease should be modified for women on HAART.

##### HPV-Associated Anal Intraepithelial Neoplasia and Anal Cancer among HIV-Infected Men Who Have Sex with Men and among Women

Evidence from multiple studies demonstrates that HIV-infected men who have sex with men, and HIV-infected women are at increased risk for anal high-grade squamous intraepithelial lesions (HSIL) and might be at increased risk for anal cancer. In view of this evidence, and given a cost-effectiveness analysis projecting that screening and treatment for anal HSILs provide clinical benefits comparable to other measures to prevent opportunistic infections (OIs) among HIV-infected persons, anal cytology screening of HIV-infected men who have sex with men and of women might become a useful preventive measure. However, studies of

screening and treatment programs for anal HSILs need to be implemented before recommendations for anal cytology screening can be made.

## **Treatment Recommendations**

### *Treatment of Disease*

#### Genital Warts

Multiple treatments for HPV-associated skin and external genital lesions exist; however, no single treatment is ideal for all patients or all lesions **(CIII)**. Standard topical therapy for HPV-associated lesions among HIV-infected children is often ineffective. Treatment can induce wart-free periods, but the underlying viral infection can persist and result in recurrence. No data suggest that treatment modalities for external genital warts should be different in the setting of HIV infection. However, persons who are immunosuppressed because of HIV might have larger or more numerous warts, might not respond as well as immunocompetent persons to therapy for genital warts, and might have more frequent recurrences after treatment. In addition, topical treatments are seldom effective in patients with large or extensive lesions. Topical treatments include podofilox (0.5 %) solution or gel (antimitotic agent), imiquimod (5%) cream (topical immune enhancer that stimulates production of interferon and other cytokines), trichloroacetic or bichloroacetic acid (80%–90% aqueous solution) (caustic agents that destroy warts by chemical coagulation of proteins), and podophyllin resin (10%–25%) in a compound tincture of benzoin (contains antimitotic compounds and mutagens). Podofilox and imiquimod are patient applied. Podofilox is applied to all lesions twice a day for 3 consecutive days, followed by 4 days of no therapy. This cycle can be repeated weekly up to 4 weeks **(BIII)**. Imiquimod is applied once daily at bedtime three times a week for up to 16 weeks. The treatment area should be washed with soap and water the following morning **(BII)**. Acid cauterization (i.e., trichloroacetic or bichloroacetic acid) and podophyllin resin require application by a health care provider. Acid cauterization should be discontinued if substantial improvement is not observed after three treatment sessions or complete clearance has not occurred after six consecutive treatments **(BIII)**. Podophyllin resin is applied and removed by washing a few hours later; applications can be repeated weekly for up to 6 weeks **(CIII)**. Podophyllin resin has lost favor since the production of the resin can vary in potency and is not reliable.

Other treatments include Veregen (based on the antioxidative effect of green tea extract), intralesion interferon or 5-fluorouracil/epinephrine gel implant, and cidofovir topical gel (1%). Veregen (sin catechins) is a new FDA-approved topical product for external genital wart treatment that can be used three times daily for up to 16 weeks. No data are available on this treatment for HIV-infected persons **(CIII)**. Cidofovir topical gel (1%) is a topical preparation that has been evaluated in a limited number of adults for treatment of anogenital HPV infection **(CIII)**. Topical cidofovir may result in systemic absorption and be associated with renal toxicity. Injectable therapy (e.g., interferon or 5-fluorouracil/epinephrine gel implant) should be offered in only severely recalcitrant cases due to inconvenient routes of administration, frequent office visits, and a high frequency of systemic adverse effects.

Lesions can be removed by cryotherapy or surgery (**BIII**). Cryotherapy (i.e., application of liquid nitrogen or dry ice) must be applied until each lesion is thoroughly frozen. Treatment can be repeated every 1 to 2 weeks up to four times. The major toxicity is local pain. Adequate local pain management for all caustic treatments in children is essential. Topical anesthetics such as eutectic mixture of local anesthetics (EMLA) are favored. Surgical removal either by tangential scissor, tangential shave excision, curettage, or electrosurgery can be performed.

### Oral Warts

Oral warts may be located on a variety of surfaces in the mouth. In contrast to other oral manifestations of HIV, an increased prevalence of oral warts in patients on HAART has been reported from the United States and the United Kingdom. There are no randomized trials of treatment of oral warts. Treatments include surgical excision and cryotherapy; some topical modalities have had success.

### Respiratory Papillomatosis

Respiratory papillomatosis should be managed by a specialist. Treatment is directed toward removing lesions obstructing the airway rather than at the elimination of disease. Lesions are removed by debridement or laser. Systemic interferon-alfa therapy or intralesional cidofovir has been used as an investigational treatment with limited success in children with frequent recurrences or extension into the trachea, bronchi, or lung parenchyma (**CIII**).

### Management of Abnormal Cytology

Management of anogenital HPV infection accompanied by cytologic changes indicating dysplasia/carcinoma among adolescents is slightly altered from that for the adult population. Adolescents aged 13 to 20 years and young women are considered a special population. There is a very low risk for invasive cervical cancer in this group, but CIN lesions are common. As noted earlier, CIN in HIV-uninfected adolescents also has a very high rate of spontaneous regression of CIN lesions. HPV testing for follow-up is not recommended for adolescent populations whether HIV infected or uninfected.

Because of the high rate of progression to HSIL, it is currently recommended to refer all HIV-infected adolescents with any squamous intraepithelial lesions (SIL) (low-grade squamous intraepithelial lesions [LSIL] or HSIL) and atypical squamous cells of undetermined significance (ASCUS) suggestive of HSIL to colposcopy (**BIII**). In patients with ASCUS alone, Pap smear for cytology can be repeated in 6 to 12 months. If ASCUS or greater is found on repeat cytology, referral to colposcopy is warranted.

### Treatment of Histologic CIN

Follow-up with annual cytological assessment is recommended for adolescents with CIN 1 (**AII**). At the 12-month follow-up, only adolescents with HSIL or greater on the repeat cytology should be referred to colposcopy. At the 24-month

follow-up, those with an ASCUS or greater result should be referred to colposcopy **(AII)**.

For adolescents and young women with a histological diagnosis of CIN 2 or 3 not otherwise specified, either treatment or observation for up to 24 months using both colposcopy and cytology at 6-month intervals is acceptable, provided colposcopy is satisfactory **(BIII)**. When a histological diagnosis of CIN 2 is specified, observation is preferred but treatment is acceptable. When a histological diagnosis of CIN 3 is specified or when colposcopy is unsatisfactory, treatment is recommended **(BIII)**.

If the colposcopic appearance of the lesion worsens or if HSIL cytology or a high-grade colposcopic lesion persists for 1 year, repeat biopsy is recommended **(BIII)**. After two consecutive "negative for intraepithelial lesion or malignancy" results, adolescents and young women with normal colposcopy can return to routine cytological screening **(BII)**. Treatment is recommended if CIN 3 is subsequently identified or if CIN 2 or 3 persists for 24 months **(BII)**.

Persistent CIN 1, 2, and 3 lesions in HIV-infected women should be treated as in HIV-uninfected women. Conventional therapies used for treatment of CIN 2 or 3 include cryotherapy, laser therapy, cone biopsy, and a loop electrosurgical excision procedure (LEEP). LEEP is generally the preferred mode of treatment **(BIII)**. Recurrence rates of 40% – 60% after treatment have been reported among HIV-infected women undergoing these procedures. Pregnant HIV-infected adolescents should be treated similarly to pregnant HIV-infected adults.

#### Role of Antiretroviral Therapy (ART)

HAART has not been consistently associated with a reduced risk for HPV-related cervical abnormalities in HIV-infected women. However, severe immunosuppression is associated with greater frequency of morbidity and mortality.

#### *Monitoring of Adverse Events, Including Immune Reconstitution Inflammatory Syndrome*

Monitoring is required during and after treatment of genital warts since each of the treatments has associated toxicity and recurrences are common after treatment. Patients can be monitored by physical examination for evidence of recurrence. The major toxicity of podophyllotoxin and topical podophyllin resin is local skin irritation. Also, if podophyllin is applied to a large treatment area, systemic absorption can cause nausea, vomiting, and CNS effects. The major toxicity of imiquimod is inflammation at the application site. The major toxicity of cryotherapy is local pain. The major side effects of surgical treatment for genital warts are local pain, bleeding, and secondary infection. The major adverse events associated with acid cauterization are local pain and irritation or ulceration of adjacent normal skin. Intralesional interferon can be associated with systemic toxicities of interferon, including fever, fatigue, myalgia, malaise, depression, and other influenza-like symptoms. Infrared coagulation may lead to bleeding and abscess formation. Scarring may occur with any of the above treatment modalities. Topical cidofovir may result in systemic absorption and be associated

with renal toxicity. Secondary infections are not uncommon if ulcerations occur. Patients should be monitored regularly after each treatment.

Because risk of recurrence of CIN and cervical cancer after conventional therapy is increased among HIV-seropositive persons, patients should be carefully followed after treatment with frequent cytologic screening and colposcopic examination according to published guidelines **(AII)**. Treatment of CIN with ablative and excisional modalities can be associated with several adverse events such as pain and discomfort, intraoperative hemorrhage, postoperative hemorrhage, infection, and cervical stenosis.

The major toxicity of topical agents for treatment of external genital warts is local pain or irritation of adjacent normal skin. HIV-infected patients with immunosuppression might have a lower response rate to all of these modalities. Secondary infections are not uncommon if ulcerations occur. Patients should be monitored regularly after each treatment.

Because of the frequent recurrence of SIL after treatment, close surveillance with colposcopy and cytology is recommended.

An "immune reconstitution"-like syndrome related to the occurrence of HPV-associated oral warts among HIV-infected adults has been observed in which the occurrence of oral warts was associated with a decrease in HIV RNA levels with HAART. Immune reconstitution in response to viral load reduction might result in a return of marked inflammatory responses against latent oral HPV infection.

#### *Management of Treatment Failure*

Treatment failure is defined as the persistence or recurrence of lesions after appropriate therapy. For persistent or recurrent genital warts, retreatment with any of the modalities previously described should be considered, preferably with an alternative modality to the one that previously failed **(AIII)**. Genital warts often require more than one course of treatment. Recalcitrant warts should be managed by experienced clinicians and referred for excisional therapy. Recurrence of CIN may require additional treatments (i.e., LEEP, laser).

#### **Prevention of Recurrence**

There are no recommendations for prevention of recurrence of external genital warts. Patients should be monitored with cytologic screening according to published guidelines and, when indicated, colposcopic examination for recurrent lesions **(AI)**. Use of low-dose intravaginal fluorouracil (Efudex) was shown in one study to reduce recurrence of CIN after LEEP but lack of additional studies do not warrant routine use. Efudex should not be used in pregnant women.

#### *Discontinuing Secondary Prophylaxis*

Not applicable.

#### **Viral Infections: Progressive Multifocal Leukoencephalopathy (PML)**

## **Prevention Recommendations**

### *Preventing Exposure*

There is no known means of preventing exposure to Jamestown Canyon virus (JCV).

### *Preventing First Episode of Disease*

There is no means of preventing the occurrence of PML in severely immune-suppressed persons. The use of HAART can prevent or reverse the development of severe immunosuppression.

### *Discontinuing Primary Prophylaxis*

There is no demonstrated means of primary prophylaxis of JCV infection or the development of PML.

## **Treatment Recommendations**

### *Treatment of Disease*

No established effective therapy of JCV or PML exists. Survival in HIV-infected adults with PML has substantially improved in the post-HAART era, with a median survival increase from 14 to 64 weeks. A CD4 count of  $>100$  cells/mm<sup>3</sup> at the time of diagnosis of PML was associated with an improved survival, and the use of HAART post-diagnosis of PML was also strongly associated with an improved survival. Thus, the main approach to treatment involves maximally optimizing antiretroviral therapy to reverse the immunosuppression that interferes with the normal host response to this virus **(AII)**.

A number of agents have been proposed or reported anecdotally as more specific treatments for PML, but none of these has been proven effective after greater scrutiny or more extensive study. For PML, there has been a randomized open-label trial of intravenous and intrathecal cytosine arabinoside and a nonrandomized, open-label trial of cidofovir; neither drug was effective in producing clinical improvement and neither is routinely recommended **(DII)**. Immunomodulatory approaches, such as interferon-alfa, have also been described in case reports in HIV-infected adults, but none have yet been studied in a prospective, controlled clinical trial and in one analysis did not provide any benefit beyond that observed with HAART; thus they are also not currently routinely recommended **(DIII)**.

### *Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome*

Neurologic stability or improvement and prolonged survival are associated with a reduction in JCV DNA and appearance of JCV-specific antibody in CSF of HAART-treated PML patients.

When antiretroviral therapy is initiated and CD4 counts rise, certain patients will experience neurologic improvement and others might become neurologically stable; however, reports have documented patients experiencing worsening neurologic manifestations after initiation of HAART. In certain instances, this worsening is caused by an IRIS, examples of which have occurred in children. Other cases may represent the natural history of PML. The underlying etiology and trigger of HAART-associated PML is controversial. One hypothesis postulates a reduction in inhibitory cytokines (e.g., interferon-alfa and interleukin-12) after HAART, thus promoting JCV reactivation within the brain or by increasing trafficking of JCV-infected peripheral lymphocytes into the brain. JCV infection occurring coincidental to the time of HAART onset resulting in a beneficial inflammatory response with lack of disease progression is another hypothesis, particularly given that JCV in children with perinatal HIV infection would most often be acquired during childhood. The overall prevalence of IRIS in children is not known. Inflammatory PML should be suspected in HAART-treated children with advanced HIV disease who show acute neurologic deterioration and contrast-enhancing demyelinating lesions on magnetic resonance imaging (MRI).

#### *Management of Treatment Failure*

PML remission with HAART may take several weeks and there are no defined criteria to define progression of disease. A working definition used for HIV-infected adults is continued clinical worsening and continued detection of CSF JCV at 3 months (see the NGC summary of [Guidelines for the Prevention and Treatment of Opportunistic Infections in HIV-Infected Adults](#)). As noted, some patients' PML worsens despite the use of HAART, either as a result of IRIS or the natural history of PML. In both cases, HAART should be continued. If there is failure to suppress HIV RNA or to boost the CD4 count with the HAART regimen, then attention should be focused on modifying and optimizing the antiretroviral treatment **(AII)**. However, in HIV-infected children responding well to HAART but with continued worsening PML, consultation with an expert in pediatric HIV infection should be obtained.

#### **Prevention of Recurrence**

The main preventive measure, based on its role in reversing the disease, is an effective antiretroviral regimen that suppresses HIV viremia and maintains CD4 count **(AII)**.

#### *Discontinuing Secondary Prophylaxis*

There is no demonstrated means of secondary prophylaxis of JCV infection or the development of PML.

#### **Viral Infections: Varicella-Zoster Virus (VZV)**

#### **Prevention Recommendations**

##### *Preventing Exposure*

HIV-infected children and adults without evidence of immunity to VZV (with no history of varicella or zoster; or who are seronegative for VZV by a sensitive, specific antibody assay; or who lack evidence of age-appropriate vaccination) should avoid exposure to persons with varicella or zoster **(AII)**. Household contacts of HIV-infected persons without evidence of immunity should receive varicella vaccine if they lack evidence of immunity (i.e., have no history of varicella or zoster, are seronegative for HIV, were born in the United States after 1980, or lack evidence of age-appropriate vaccination) so that they will be less likely to transmit wild-type VZV to their HIV-infected contacts **(AIII)**.

### *Preventing Disease*

#### Varicella

HIV-infected children aged 1 to 8 years in Centers for Disease Prevention and Control (CDC) clinical categories N, A, and B and whose CD4 levels are  $\geq 15\%$  should be considered for vaccination (two doses of monovalent single-antigen varicella vaccine); first dose administered at age 12 to 15 months and the second dose 3 months later **(BII)**. Limited data from a clinical trial in HIV-infected children with these characteristics indicate that the vaccine was well tolerated and that  $>80\%$  of subjects had detectable VZV-specific immune response (either antibody or cell immune response or both) at 1 year after immunization. Data are not available regarding safety, immunogenicity, or efficacy of MMRV vaccine in HIV-infected children, and MMRV vaccine should not be administered as a substitute for the single-antigen varicella vaccine when vaccinating HIV-infected children.

Data on use of varicella vaccine in older HIV-infected children and adolescents are lacking. However, on the basis of expert opinion, the safety of varicella vaccine in HIV-infected persons aged  $>8$  years with similar levels of immune function (e.g., CD4 count  $\geq 200$  cells/mm<sup>3</sup>) is likely to be similar to that of children aged  $<8$  years. Immunogenicity might be lower in older HIV-infected children, adolescents, and adults. However, weighing the risk for severe disease from wild-type VZV and potential benefit of vaccination, vaccination (two doses of single-antigen vaccine, administered 3 months apart) for persons with CD4 count  $\geq 200$  cells/mm<sup>3</sup> in these age groups may be considered **(BIII)**.

The vaccine is very well tolerated by HIV-infected children; as in healthy children, serious vaccine-related adverse events are rare. As with healthy children, vaccinated HIV-infected children who develop mild rashes  $>2$  weeks after immunization rarely require antiviral therapy for Oka VZV. These rashes usually clear in 3 to 5 days without treatment. If vaccination of HIV-infected persons results in more severe clinical disease, the use of acyclovir to treat the Oka vaccine strain of VZV (which is sensitive to acyclovir) might modify the severity of disease. VZV rashes developing  $<2$  weeks after immunization, however, are usually due to wild-type VZV.

HIV-infected children with low CD4 levels ( $<15\%$ ) may develop pneumonia and neurologic manifestations from VZV and should not be immunized against varicella **(EIII)**. Immunization of such children following reconstitution of their immune system (CD4 percentage  $\geq 15\%$ ) with antiretroviral therapy, however, can be considered. Zoster from the vaccine (Oka strain) has been reported in

healthy children and in children with acute lymphocytic leukemia, but it has not yet been described in HIV-infected children.

As yet, efficacy studies on prevention of varicella in HIV-infected children are not available. The effectiveness of varicella vaccine in immunized healthy children (after one dose) and those with underlying leukemia (after two doses) is about 80% – 85% prevention of clinical infection, with modified varicella in most of the remainder.

For post-exposure prophylaxis against varicella, HIV-infected children and adolescents who lack evidence of immunity to VZV (i.e., with no history of varicella or zoster; or who are seronegative for VZV by a sensitive, specific antibody assay; or who lack evidence of age-appropriate vaccination) should be passively immunized as soon as possible and in <96 hours after close contact with a person with varicella or zoster **(AIII)**. Previously this was performed by administering varicella-zoster immune globulin (VZIG). Licensure of varicella vaccine in the United States has resulted in dramatically fewer requests for VZIG; therefore, VZIG is no longer being produced. A new product, human varicella immune globulin (VariZIG), manufactured in Canada, is the replacement. VariZIG is a lyophilized presentation which, when properly reconstituted, is approximately a 5% solution of IgG that can be administered intramuscularly. VariZIG is available under an investigational new drug application expanded access protocol (available at <http://www.fda.gov/cber/infosheets/mphvzig020806.htm>). VariZIG can be obtained in the United States, and it has received central institutional review board (IRB) approval, but local IRB approval may also be necessary. VariZIG can be obtained 24 hours a day from the sole authorized U.S. distributor (FFF Enterprises, Temecula, California) at 1-800-843-7477 or online at [FFF Enterprises](http://www.fffenterprises.com). An alternative to VariZIG for passive immunization is IVIG 400 mg/kg, administered once. IVIG should also be administered within 96 hours of exposure.

Data are lacking regarding the effectiveness of acyclovir for preventing varicella among susceptible HIV-infected children. There is minimal published information on this form of prophylaxis for healthy children. If VariZIG is not available or >96 hours have passed since exposure, some experts recommend prophylaxis with acyclovir (80 mg/kg/day, administered four times per day for 5 to 7 days; beginning from Day 7 to Day 10 after exposure, maximum dose of 80 mg, four times per day). However, the use of acyclovir for prophylaxis in HIV-infected VZV-exposed children has not been studied. For that reason, some experts would consider it prudent to wait until the first appearance of rash to start acyclovir therapy for the VZV-susceptible and -exposed HIV-infected child to whom passive immunization was not given **(CIII)**.

## **Treatment Recommendations**

### *Treatment of Disease*

On the basis of controlled trials among children with malignancies, acyclovir is the drug of choice for treatment of VZV infection among HIV-infected children **(AI)**. For varicella, acyclovir should be initiated as soon as possible after initial lesions appear. New lesions can continue to appear for 72 hours after initiation of acyclovir and crusting of all lesions might take 5 to 7 days. Intravenous acyclovir

is recommended for treatment of primary varicella among HIV-infected children with severe immunosuppression (i.e., CD4 <15%, CDC Immunologic Category 3) or who have high fever or numerous or deep, necrotic, or hemorrhagic skin lesions **(AIII)**. For children aged <1 year, the dose of acyclovir is 10 mg/kg/dose administered intravenously every 8 hours as a 1-hour infusion. Some health care providers administer the same dose for children aged ≥1 year, and others use acyclovir based on body surface area among children aged ≥1 year old (500 mg/meter<sup>2</sup> body surface area/dose intravenously every 8 hours as a 1-hour infusion). Administration is for 7 to 10 days or until no new lesions have appeared for 48 hours. Oral administration should be used only for treatment of primary varicella among HIV-infected children with normal or only slightly decreased CD4 counts (CDC Immunologic Category 1 or 2) who have mild varicella disease **(BIII)**.

Acyclovir is the treatment of choice for zoster among HIV-infected children, administered for 7 to 10 days, although longer durations of therapy should be considered if lesions are slow to resolve **(AII)**. With zoster, oral acyclovir can be administered because the chance for disseminated, life-threatening disease is less with zoster than varicella. Initial intravenous administration should be considered for HIV-infected children with severe immunosuppression (i.e., CD4 <15%, CDC Immunologic Category 3), trigeminal nerve involvement, or extensive multidermatomal zoster **(AII)**. If cutaneous lesions are extensive or if clinical evidence of visceral involvement is observed, intravenous acyclovir should be initiated and continued until cutaneous lesions and visceral disease are clearly resolving **(AII)**, then change to oral administration can be considered to complete the course of therapy (10 to 14 days in this situation) **(AIII)**. Doses of acyclovir for the treatment of zoster are the same as those for varicella.

Progressive outer retinal necrosis is rapidly progressive and leads to profound loss of vision; prognosis for visual preservation is poor despite aggressive therapy and optimal therapy is yet to be defined. Regardless of specific VZV antiviral therapy, optimization of antiretroviral therapy is also recommended. Some experts recommend anti-VZV therapy that includes a combination of intravenous ganciclovir (5 mg/kg/dose given intravenously every 12 hours) and foscarnet (90 mg/kg/dose given intravenously every 12 hours) plus twice-weekly intravitreal injections of ganciclovir (2 mg/0.05 mL and/or foscarnet 1.2 mg/0.05 mL) **(BIII)**. In contrast, acute retinal necrosis appears more responsive to antiviral therapy, and one recommended treatment is high-dose intravenous acyclovir (10–15 mg/kg intravenously every 8 hours for 10 to 14 days), followed by prolonged (i.e., 4 to 6 weeks) oral valacyclovir **(AIII)**. Involvement of an ophthalmologist experienced with management of patients with VZV retinitis is strongly recommended **(AIII)**.

Alternatives to acyclovir in older adolescents and adults include valacyclovir and famciclovir. Valacyclovir is a prodrug of acyclovir with improved bioavailability that is rapidly converted to acyclovir after absorption and is approved for treatment of zoster in adults. It is not active against acyclovir-resistant VZV strains. Data are limited for its use in children; bioavailability is about 45% and independent of age in children. Based on limited available data, pediatric blood levels of acyclovir (from the prodrug valacyclovir) similar to that of valacyclovir tablets in adults can be achieved by administering an oral dose of valacyclovir of 20–25 mg/kg/dose given two or three times a day **(CIII)**. However, valacyclovir is available only in a

caplet formulation, and hence this drug is an alternative only for children old enough to swallow the valacyclovir caplets. Although tablets can be crushed, they have a very unpleasant taste. A liquid formulation that is stable for 21 days can be prepared in Ora-Sweet and Syrpalta syrups and stored in amber glass bottles.

Famciclovir is the oral prodrug of penciclovir. It is not active against acyclovir-resistant VZV strains. It is comparable in efficacy to oral acyclovir in treatment of immunocompromised adults with localized zoster, although it has not been approved for this indication. It is available only in tablet form. There are no specific data on the pharmacokinetics and dosing of famciclovir in children and no pediatric preparation is available.

#### *Monitoring and Adverse Events, Including Immune Reconstitution Inflammatory Syndrome*

Acyclovir is primarily excreted by the kidney, and dose adjustment (based on creatinine clearance) is needed among patients with renal insufficiency or renal failure. Primary toxicities of acyclovir are phlebitis, renal toxicity, nausea, vomiting, and rash. Toxicities are similar for valacyclovir. Among infants receiving high-dose acyclovir for neonatal HSV disease, the major toxicity was neutropenia (absolute neutrophil count  $<1,000/\text{mm}^3$ ), which was observed in 21% of children. Grade 3 or higher nephrotoxicity was observed in 6% of children. For children receiving high-dose IV acyclovir, monitoring of renal function is recommended at initiation of treatment and once or twice weekly for the duration of treatment, particularly for those with underlying renal dysfunction or those receiving prolonged therapy.

In HIV-infected adults, immune reconstitution following initiation of HAART may be associated with an increased frequency of VZV reactivation. VZV-associated IRIS following HAART has also been described in HIV-infected children. In a study in 153 HAART-treated children in Thailand, 19% of children starting HAART experienced IRIS; 22% of the cases of IRIS were secondary to VZV. In the reported cases, manifestations were cutaneous and generally mild, manifested as VZV reactivation in a typical dermatomal distribution of vesicular lesions, and responded well to treatment with oral acyclovir. Most cases present in the first 4 months of HAART; the median time from the initiation of HAART to the onset of clinical symptoms in the Thai children was 6 weeks (range: 2 to 21 weeks).

#### *Management of Treatment Failure*

Children who continue to develop lesions or whose lesions fail to heal after 10 days of treatment may be infected with acyclovir-resistant VZV. If possible, a culture should be obtained to analyze the virus for drug resistance. HIV-infected children with acyclovir-resistant VZV can be treated with intravenous foscarnet for 7 days or until no new lesions have appeared for 48 hours (**AII**). The dose of foscarnet should be administered slowly over the course of 2 hours (i.e., no faster than 1 mg/kg/minute). Infusing foscarnet with saline fluid loading can minimize renal toxicity. Doses should be modified among patients with renal insufficiency.

The main toxicity of foscarnet is decreased renal function;  $\leq 30\%$  of patients experience an increase in serum creatinine levels. Renal toxicity and foscarnet binding to divalent metal ions (e.g., calcium) lead to metabolic abnormalities in

approximately one-third of patients, and serious electrolyte imbalances (including abnormalities in calcium, phosphorus, magnesium, and potassium levels) and secondary seizures, cardiac dysrhythmias, abnormal liver transaminases, and CNS symptoms can occur.

## Prevention of Recurrence

### *Preventing Recurrence*

#### Zoster

No preventive measures are available for zoster in HIV-infected children and adolescents. A vaccine for prevention of herpes zoster has been approved for use in immunocompetent adults >60 years of age. Data regarding safety and efficacy of this vaccine in HIV-infected individuals of any age are lacking and its use in HIV-infected individuals is not recommended at the present time **(DIII)**. However, prospective clinical trials to evaluate the safety and immunogenicity of herpes zoster vaccine in HIV-infected adults are planned.

### *Discontinuing Secondary Prophylaxis*

Not applicable.

## Definitions:

Rating Scheme for Prevention and Treatment Recommendations	
<b>A</b>	Both strong evidence for efficacy and substantial clinical benefit support recommendation for use. <b>Should always be offered.</b>
<b>B</b>	Moderate evidence for efficacy - or strong evidence for efficacy but only limited clinical benefit - supports recommendation for use. <b>Should generally be offered.</b>
<b>C</b>	Evidence for efficacy is insufficient to support a recommendation for or against use. Or evidence for efficacy might not outweigh adverse consequence (e.g., drug toxicity, drug interactions) or cost of the treatment under consideration. <b>Optional.</b>
<b>D</b>	Moderate evidence for lack of efficacy or for adverse outcome supports a recommendation against use. <b>Should generally not be offered.</b>

<b>E</b>	Good evidence for lack of efficacy or for adverse outcome supports a recommendation against use. <b>Should never be offered.</b>
<b>Quality of Evidence Supporting the Recommendation</b>	
<b>I</b>	Evidence from at least one randomized, controlled trial.
<b>II</b>	Evidence from at least one well-designed clinical trial without randomization, from cohort or case-controlled analytic studies (preferably from more than one center), or from multiple time-series studies. Or dramatic results from uncontrolled experiments.
<b>III</b>	Evidence from opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees.

### CLINICAL ALGORITHM(S)

None provided

## EVIDENCE SUPPORTING THE RECOMMENDATIONS

### TYPE OF EVIDENCE SUPPORTING THE RECOMMENDATIONS

The type of supporting evidence is identified and graded for most recommendations (see "Major Recommendations").

## BENEFITS/HARMS OF IMPLEMENTING THE GUIDELINE RECOMMENDATIONS

### POTENTIAL BENEFITS

Appropriate prevention and treatment of viral infections in human immunodeficiency virus (HIV)-exposed and HIV-infected children

### POTENTIAL HARMS

#### Adverse Drug Effects and Drug Interactions

Major toxicities and interactions of the drug preparations used in treatment of opportunistic infections are discussed in the "Major Recommendations" section of this summary and in Table 5 in the original guideline document. Drug interactions of clinical significance are discussed in Table 6 in the original guideline document.

## CONTRAINDICATIONS

### CONTRAINDICATIONS

A list of drug contraindications for prevention of drug interactions is provided in Table 6 of the original guideline document.

## QUALIFYING STATEMENTS

### QUALIFYING STATEMENTS

Treatment of opportunistic infections is an evolving science, and availability of new agents or clinical data on existing agents might change therapeutic options and preferences. As a result, these recommendations will need to be periodically updated.

## IMPLEMENTATION OF THE GUIDELINE

### DESCRIPTION OF IMPLEMENTATION STRATEGY

An implementation strategy was not provided.

### IMPLEMENTATION TOOLS

Personal Digital Assistant (PDA) Downloads

For information about [availability](#), see the "Availability of Companion Documents" and "Patient Resources" fields below.

## INSTITUTE OF MEDICINE (IOM) NATIONAL HEALTHCARE QUALITY REPORT CATEGORIES

### IOM CARE NEED

Getting Better  
Living with Illness  
Staying Healthy

### IOM DOMAIN

Effectiveness  
Patient-centeredness

## IDENTIFYING INFORMATION AND AVAILABILITY

### BIBLIOGRAPHIC SOURCE(S)

Viral infections. In: Centers for Disease Control and Prevention (CDC), National Institutes of Health (NIH), HIV Medicine Association of the Infectious Diseases Society of America, Pediatric Infectious Diseases Society, American Academy of Pediatrics. Guidelines for prevention and treatment of opportunistic infections among HIV-exposed and HIV-infected children. Atlanta (GA): Centers for Disease Control and Prevention (CDC); 2008 Jun 20. p. 91-146.

## **ADAPTATION**

Not applicable: The guideline was not adapted from another source.

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## **GUIDELINE DEVELOPER(S)**

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## **FINANCIAL DISCLOSURES/CONFLICTS OF INTEREST**

The Centers for Disease Control and Prevention (CDC), their planners, and their content specialists wish to disclose they have no financial interests or other relationships with the manufacturers of commercial products, suppliers of commercial services, or commercial supporters. This report does not include any discussion of the unlabeled use of a product or a product under investigational use.

## **GUIDELINE STATUS**

This is the current release of the guideline.

This guideline updates a previous version: Mofenson LM, Oleske J, Serchuck L, Van Dyke R, Wilfert C. Treating opportunistic infections among HIV-exposed and infected children: recommendations from CDC, the National Institutes of Health, and the Infectious Diseases Society of America. MMWR Recomm Rep 2004 Dec 3;53(RR-14):1-92. [422 references]

## **GUIDELINE AVAILABILITY**

Electronic copies: Available in Portable Document Format (PDF) from the [AIDSinfo Web site](#).

The guideline is also available for Palm OS or Pocket PC download from the [AIDSinfo Web site](#).

Print copies: Available from the Centers for Disease Control and Prevention, MMWR, Atlanta, GA 30333. Additional copies can be purchased from the Superintendent of Documents, U.S. Government Printing Office, Washington, DC 20402-9325; (202) 783-3238.

## **AVAILABILITY OF COMPANION DOCUMENTS**

None available

## **PATIENT RESOURCES**

None available

## **NGC STATUS**

This NGC summary was completed by ECRI on December 20, 2004. This summary was updated on January 21, 2005, following the release of a public health advisory from the U.S. Food and Drug Administration regarding the use of nevirapine. This summary was most recently updated on May 3, 2005 following the withdrawal of Bextra (valdecoxib) from the market and the release of heightened warnings for Celebrex (celecoxib) and other nonselective nonsteroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI on June 16, 2005, following the U.S. Food and Drug Administration advisories on Sustiva (efavirenz) and COX-2 selective and non-selective non-steroidal anti-inflammatory drugs (NSAIDs). This summary was updated by ECRI Institute on October 3, 2007 following the U.S. Food and Drug Administration (FDA) advisory on Rocephin (ceftriaxone sodium). This summary was updated by ECRI Institute on July 28, 2008 following the U.S. Food and Drug Administration advisory on fluoroquinolone antimicrobial drugs. This NGC summary was updated by ECRI Institute on August 25, 2009.

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